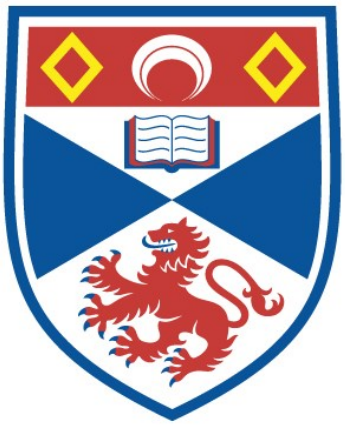
SOME REACTIONS OF UREA AND RELATED COMPOUNDS

Ishtiaq Hussain

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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SOME REACTIONS

OF

UREA AND RELATED COMPOUNDS

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN THE FACULTY OF SCIENCE OF THE

UNIVERSITY OF ST. ANDREWS

BY

ISHTIAQ HUSSAIN

ST. ANDREWS

AUGUST 1980

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IN THE NAME OF GOD,

THE COMPASSIONATE, THE MERCIFUL.

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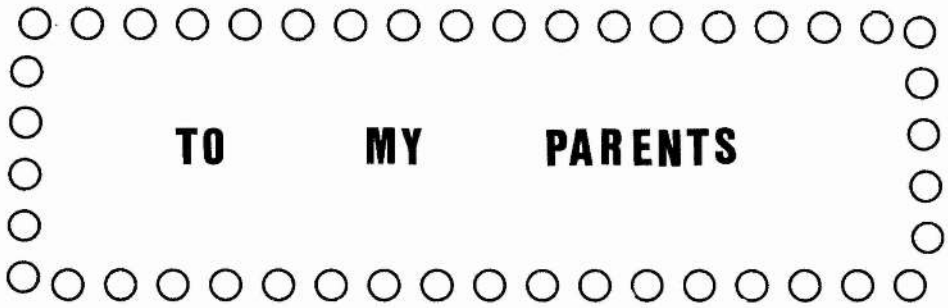
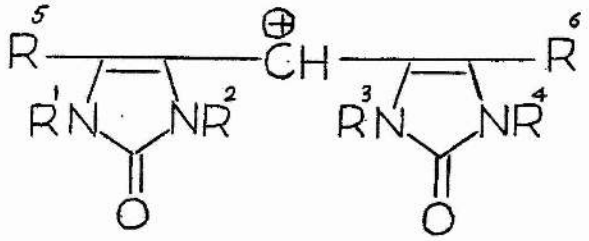

TO MY PARENTS

ABSTRACT

In this thesis reactions of urea and its N-alkyl derivatives with monoketones, α-diketones, benzladehyde, acyloins, diaminoethane and its N-alkyl derivatives, oxidation of alkyl and aryl derivatives of thiourea, nitration of Hector's Base, effect of bases on the adduct of Hector's Base, structural elucidation of Hector's Base, Dost's Base and related compounds by the application of spectral techniques, and the reaction of picric acid with creatinine in alkaline media are discussed.

Reactions of monoketones (acetone, mesityl oxide, acetophenone and benzophenone) and benzaldehyde with urea, 1-methylurea and 1,3-dimethylurea gave white crystalline products. These products were identified by proton and carbon-13 nmr techniques, physical, chemical and spectrophotometric methods wherever appropriate. A mechanism for these reactions has been proposed. In all these cases, monoketones (except benzophenone) undergo self-condensation in acid solution and the resulting products react with ureas. In the absence of ureas there is further self-condensation to yield hydrocarbons. In case of benzaldehyde reaction, it is the urea which undergoes self-condensation and resulting biuret, in turn, reacts with benzaldehyde. Moreover, it has been found that at least one methyl group adjacent to carbonyl group is involved in the self-condensation process. If methyl groups on either side of carbonyl group are replaced by phenyl groups (benzophenone) then there is no reaction.



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a $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = Me$

b $R^1 = R^4 = Me$, $R^2 = R^3 = H$, $R^5 = R^6 = Me$

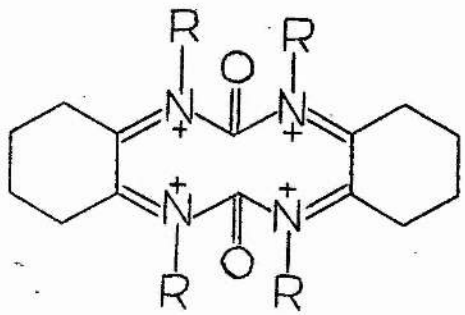
c $R^1 = R^4 = H$, $R^2 = R^3 = Me$, $R^5 = R^6 = Me$

d $R^1 = R^3 = Me$, $R^2 = R^4 = H$, $R^5 = R^6 = Me$

e $R^1 = R^2 = R^3 = R^4 = H$ $R^5 = R^6 = Me$

f $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = R^6 = Ph$

g $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = Ph$



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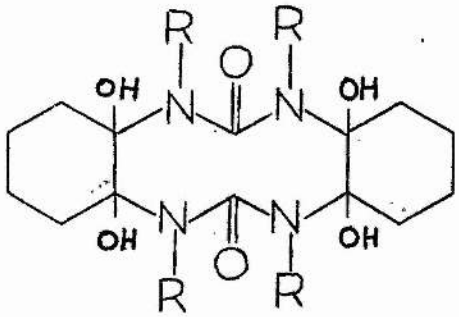
b R = H



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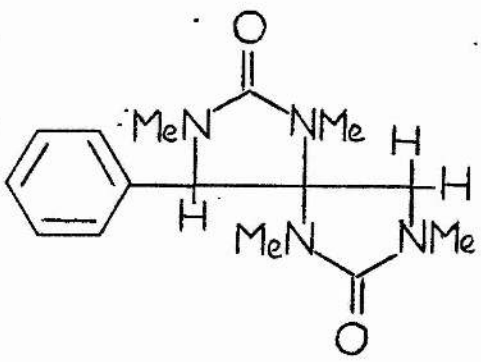

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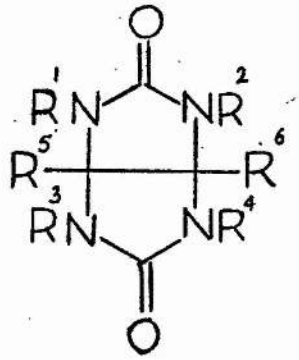

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a $R^1 = R^2 = R^3 = R^4 = H, \quad R^5 = R^6 = Me$

b $R^1 = R^2 = R^3 = R^4 = H, \quad R^5 = Ph, \; R^6 = Me$

c $R^1 = R^4 = Me, \; R^2 = R^3 = H, \; R^5 = R^6 = Me$

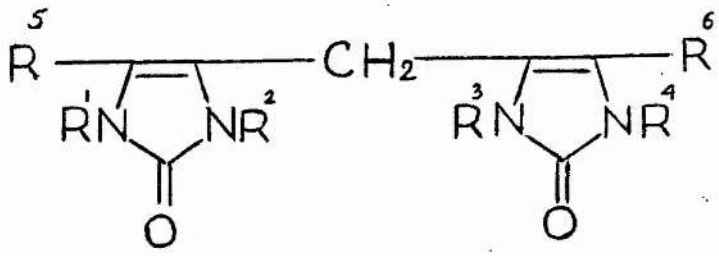
d $R^1 = R^3 = Me, \; R^2 = R^4 = H, \; R^5 = R^6 = Me$

e $R^1 = R^4 = Me, \; R^2 = R^3 = H, \; R^5 = Ph, \; R^6 = Me$

f $R^1 = R^3 = Me, \; R^2 = R^4 = H, \; R^5 = Ph, \; R^6 = Me$

g $R^1 = R^2 = R^3 = R^4 = H, \quad R^5 = R^6 = Ph$

h $R^1 = R^3 = H, \; R^2 = R^4 = Me, \; R^5 = R^6 = Ph$



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a $R^1 = R^4 = Me, \; R^2 = R^3 = H, \; R^5 = R^6 = Ph$

d $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = Me$

h $R^1 = R^2 = R^3 = R^4 = H, \quad R^5 = R^6 = Ph$

Unlike monoketones, α-diketones (butane-2,3-dione, 1-phenylpropane-1,2-dione and cyclohexane-1,2-dione) reacted readily with urea, 1-methylurea and 1,3-dimethylurea in acid solution to give intensely coloured products. These colours have been used for the determination of urea concentration present in biological fluids. The responsible protochromogens were purified either by column chromatography or fractional crystallisation. Four main products ie. (28), (33), (41) and (55), were obtained. Acidification of solution (33) gave a purple colouration, the intensity of which increased with time. The rate of colour intensification was also increased by blowing oxygen through the solution and by addition of an oxidising agent. It is a 'skipped' diene and therefore readily susceptible to radical oxidation at the methylene group to give a hydroperoxide. Protonation of this and elimination of hydrogen peroxide would give the carbonium ion (47), which is related to the cyanine dyes. The positive charge can be delocalised on one of the two outer nitrogens with formation of a conjugated, chromophoric system. Similarly, compounds (28) and (41), on heating in concentrated HCl or H_2SO_4 were converted into (33). Compound (55) is another kind of protochromogen and in acid solution yielded the tetracation (56) which is responsible for the colour. The colour intensity went on increasing with acid strength. Ethyleneurea, which is closely related to 1,3-dimethylurea, did not give colouration with α-diketones. However, it gave polymeric material with butane-2,3-dione and an intractable tar with 1-phenylpropane-1,2-dione. Reaction of cyclohexane-1,2-dione with ethyleneurea yielded a white powder and this was identified by all available means. Acyloins

(α-hydroxyketones) reacted with ureas to form 4-imidazoline-2-ones which also gave a colouration in strong acid. In this case, the cause of colour formation was not further investigated. Reaction mechanisms of all these reactions are discussed.

Besides mono and diketones, urea also reacts with diaminoethane and its N-alkyl derivatives to yield 2-imidazolidines, often known as ethyleneurea derivatives. We have found that it is the carbon-nitrogen bond of urea which breaks down during the formation of products. First, an isocyanate intermediate is formed which gives rise to a polymer. This polymer, on heating, changes to a monomer.

Oxidation of N-substituted thioureas with hydrogen peroxide, nitrous acid, bromine and benzoyl peroxide yields a 1,2,4-thiadiazole ring system. The positions of peripheral substituents (alkyl and aryl) around the thiadiazolidine ring are so puzzling that one is uncertain of the structures of the products resulting from the oxidation of thioureas. However, we have attempted to elucidate the structures of Hector's Base, Dost's Base, and related compounds by nitrogen-15 and carbon-13 nmr spectroscopy. The sensitivity of thiadiazole ring to acid depends upon the substituents. For example, with 2,4-diphenyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine and 2,4-dimethyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine, acid catalysed rearrangement is more rapid in the former than the latter. On the contrary, Hector's Base and Dost's Base do not undergo rearrangement because of their conversion into heteroaromatic

cations in acid solution. The breakage of N-S bond in these cations appears to be impossible in view of the aromaticity lost. In addition to this, Hector's Base forms addition products with a number of reagents, e.g. carbon disulphide, methyl isothiocyanate, phenyl isothiocyanate, methyl, and phenyl isocyanates. The effect of base on these adducts have also been studied. The exocyclic nitrogen of Hector's Base seems to be more basic than other nitrogens. In acid solution, this nitrogen is protonated which in turn, deactivates the phenyl ring situated at position 4. As a result, the anilino part of the molecule is nitrated. In all these cases reaction mechanisms relating to their products are discussed.

The reaction between an alkaline solution of sodium picrate and creatinine gives a red colouration, which has been used for many years in the quantitative determination of creatinine in biological fluids. But the nature of the red species formed in this reaction has never been determined with certainty. However, we were successful in isolating this species and attempted to establish its structure by the application of spectral techniques. Finally, we have also examined reactions of picric acid with pyruvic acid, hydantoin and acetone.

DECLARATION

I declare that this thesis is based on the results of experiments carried out by me, that it is my own composition, and that it has not previously been presented for a Higher Degree.

This thesis describes the results of research carried out in the Department of Chemistry of the University of St. Andrews, under the supervision of Dr. A.R. Butler, between November 1977 and August 1980.

Ishtiaq Hussain

CERTIFICATE

I hereby certify that Ishtiaq Hussain has spent twelve terms of research work under my supervision, has fulfilled the conditions of Ordinance General No. 12 and the Resolution of the University Court 1967, No. 1, and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Director of Research

ACKNOWLEDGEMENT

I am highly indebted to Dr. A.R. Butler for suggesting this topic of research and for his help, encouragement and guidance throughout this work.

I wish to express my gratitude to Professor Lord Tedder for permission to use the excellent research facilities of the Department of Chemistry. My thanks also go to Dr. Douglas Lloyd and Dr. C. Glidewell for helpful discussions .

I would like to thank all technical staff of the Chemistry Department for the high quality services they provided, especially Mrs. M. Smith (nmr), Mr. C. Millar (mass spectra) and Mrs. S. Smith (microanalysis). I will not forget Mr. Charles Tüchel whose fascinating smile and beautiful little jokes always removed the obnoxious smell of chemicals from my mind whenever I went to the store to collect goods. I am also grateful to Mrs. W. Pogorzelec for typing this thesis.

My thanks are also due to all my research colleagues, friends, and flat-mates, especially Mr. Mahmood (Iran), Dr. H. Sing (India), Mr. V. Chaipanich (Thailand), Mr. Mateen (Bangladesh), Mr. J. Arroyo (Peru), Mr. Mashoor, Mr. H.A. Kifli and Mrs. Atasha (Malaysia) for their happy co-operation during my stay in St. Andrews.

Finally, I gratefull acknowledge financial assistance from the Government of Pakistan and the University of the Punjab, Lahore, Pakistan.

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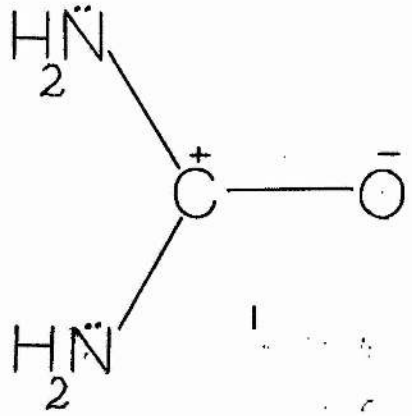
CHAPTER 1

Reaction of urea, 1-methylurea, and 1,3-dimethylurea with acetone, mesityloxide, acetophenone, benzophenone, and benzaldehyde.



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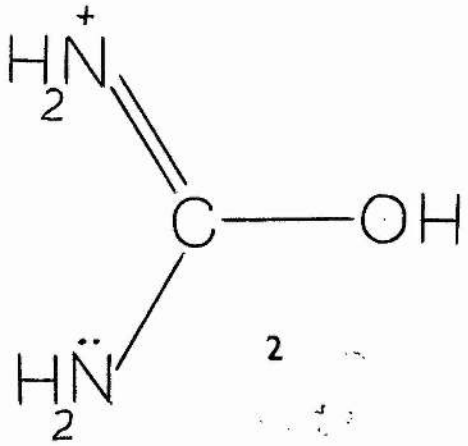

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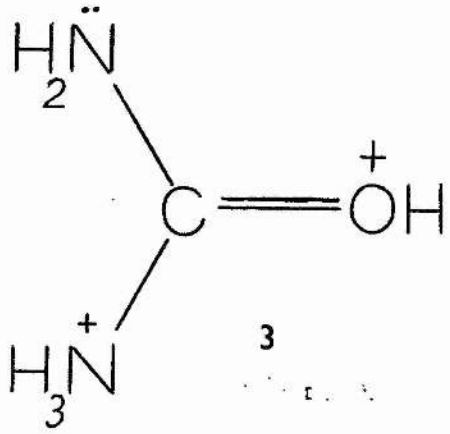


3

INTRODUCTION

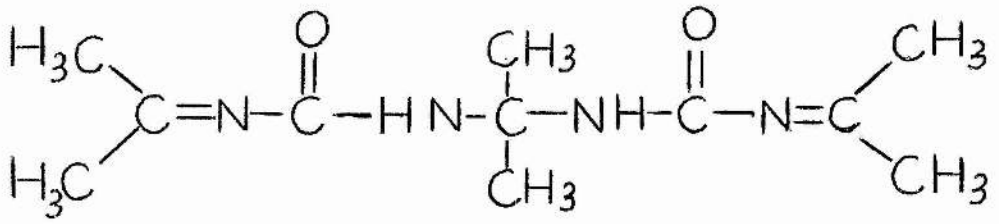
Urea is of historical interest in the development of organic chemistry. It was discovered in urine by Rouelle in 1773 (Sidgwick, 1966) and the German Chemists Wöhler (1828) reported its synthesis from inorganic starting material. Davy in 1812 (Sidgwick, 1966) prepared urea by the reaction of phosgene with ammonia, but he did not identify the product of reaction. It was recognised by Dumas (Sidgwick, 1966) as being the amide of carbonic acid. X-Ray data, dielectric constant measurements, and other evidence are strongly in favour of a mesomeric structure where the dipolar form (1) makes a significant contribution (Sidgwick, 1966).

The mesomeric structures for urea suggest that O-protonation is more likely than N-protonation. The former results in a cation that is itself resonance stabilised (2). This has been confirmed by proton nmr (Katritzky and Jones, 1961; Redpath and Smith, 1962; Olah and White, 1970; Fraenkel and Franconi, 1960; Gillespie and Birchall, 1963; Stewart and Muenster, 1961) and carbon-13 nmr studies (Butler and Glidewell, 1978). There is evidence from nitrogen-15 nmr studies that formation of the diprotonated form (3) may occur (Levy and Lichter, 1979).

However, in the present study of the reactions of urea and its N-alkyl derivatives with monoketones under acidic conditions it has been assumed that it is the oxygen of urea which is protonated. The presence of a carbonyl group adjacent to the attacking amino group

makes the nitrogen atom less basic. Because of the weak nucleophilicity of amides, catalysis is important. Reaction also often requires activated carbonyl compounds (Newallis and Rumanowski, 1964) and heating at relatively high temperatures, especially with monoketones.

Urea readily condenses with a number of aldehydes (Kilner and Samuel, 1960; Schiff, 1869; Ogata et al, 1965, 1966) but exhibits a little tendency to react with monoketones because the alkyl groups have an electron-repelling effect and decrease the polarisation of the carbonyl group. Similarly, the presence of electron-withdrawing groups adjacent to the carbonyl group (as in halogenated ketones) will increase the polarisation of the carbonyl group. Acetone and acetophenone exist predominantly in the keto form in acid solution and undergo self-condensation to give mesityl oxide and dypnone with elimination of water, which subsequently react with ureas. In the absence of ureas there is further self-condensation to yield phorone, isophorone and 1,3,5-triphenylbenzene. This chapter is concerned with a study of the reactions of urea, 1-methyl-urea, and 1,3-dimethylurea with acetone, mesityl oxide, acetophenone, benzophenone, and finally with benzaldehyde.



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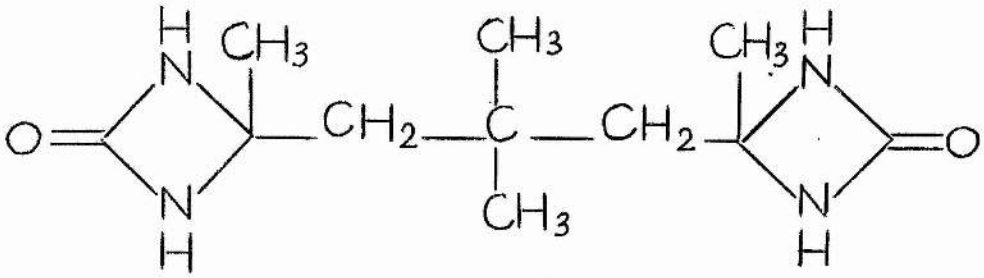

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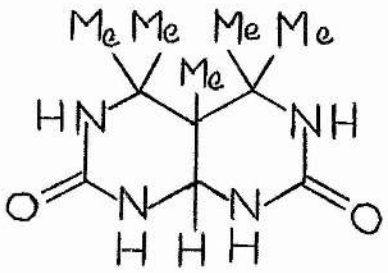

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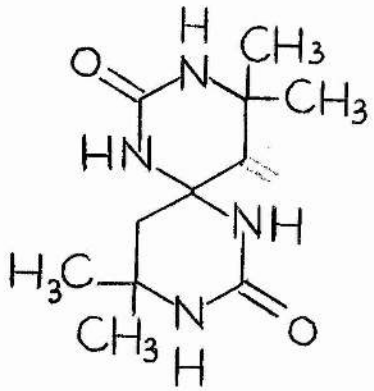

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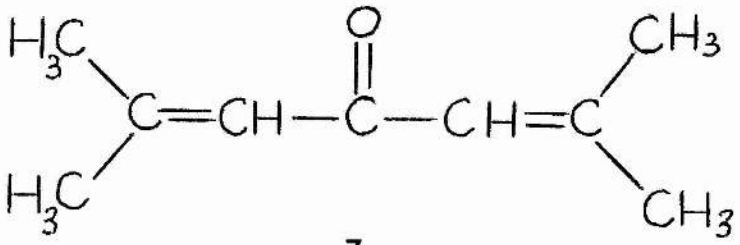

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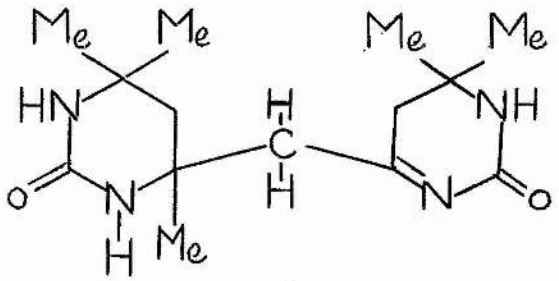
RESULTS AND DISCUSSION

Reactions with acetone and mesityloxide

The reaction of acetone with urea has been examined several times previously and different structures have been proposed for the reaction product. The first report appears to be that of Weinschenk (1901) who suggested (4) on the grounds that alkaline hydrolysis gave acetone, ammonia, and CO_2. Harvey (1952) proposed (5) in a patent. On the basis of spectral evidence Hatt and Triffett (1965) and Zigeuner et al (1966) proposed a hydropyrimidine (6). This is supported by the observation that (6) can be obtained by reaction of phorone (7) and urea. According to Hatt and Triffett (1965) there is a doublet in the 60 MHz proton nmr spectrum in D_2O solvent (80^o), at δ 1.30 (12H) ppm; and this splitting is difficult to understand. More recently Inoi et al (1966) proposed (8). In their proton nmr spectrum the two pairs of geminal methyl protons appear as a singlet, at δ 1.56 ppm; but for the second singlet, 2.40 ppm, it had to be assumed that the chemical shifts of the other methyl protons and the proton at the bridgehead were identical, which is unlikely.

We prepared the product of reaction of urea and acetone and confirmed its molecular formula. The proton nmr spectrum in trifluoroacetic acid was, in general, consistent with (6), but a molecular model indicated that the methyl groups of each geminal pair were not in the same environment (which should lead to two singlets, of equal intensity, not a doublet as noted by Hatt and Triffet (1965)) and



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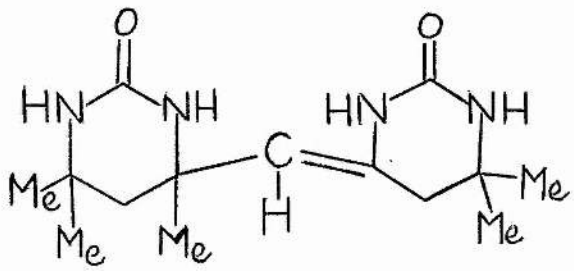

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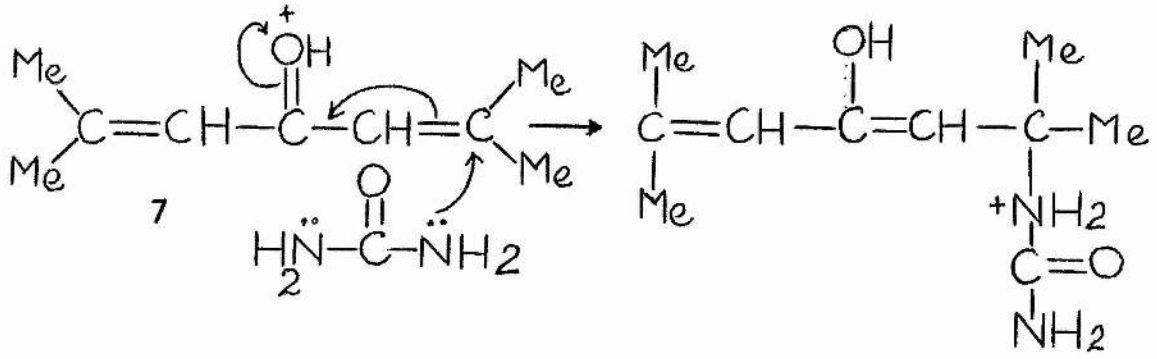
there should also be geminal splitting of the two methylene protons. When the proton nmr spectrum in [$^2H_6$]DMSO at 120° was recorded, these features were observed. There were two equal singlets at δ 1.15 and 1.18 ppm and a distorted double doublet centred at 1.89 ppm (J_{gem} 14 Hz). The carbon-13 nmr spectrum supported (6), rather than any other proposed structure. Apart from the methyl groups and carbonyl groups there are only three different carbon atoms in (6) and the noise-decoupled spectrum had peaks at δ 48.01, 52.98 and 63.32 ppm. In the off-resonance spectrum the first became a triplet and the other two remained as singlets. We conclude, therefore, that (6) is the correct structure.

Acid hydrolysis of the acetone-urea adduct gave a compound of molecular formula $C_{14}H_{24}N_4O_2$, for which Hatt and Triffett (1965) proposed structure (9), without any knowledge of the nmr spectrum. The same compound is obtained by the reaction of mesityl oxide and urea and we prepared a sample in this manner. The proton nmr spectrum in trifluoroacetic acid has three very close up-field singlets (15H), two distorted double doublets (4H), suggesting two methylene groups in different environments, and one singlet olefinic proton. These data are not in agreement with (9) but suggest, instead, structure (10). This structure was confirmed by the noise-decoupled carbon-13 nmr spectrum. Apart from the methyl groups, the spectrum indicated at least nine different carbon atoms and the shifts were consistent with structure (10).



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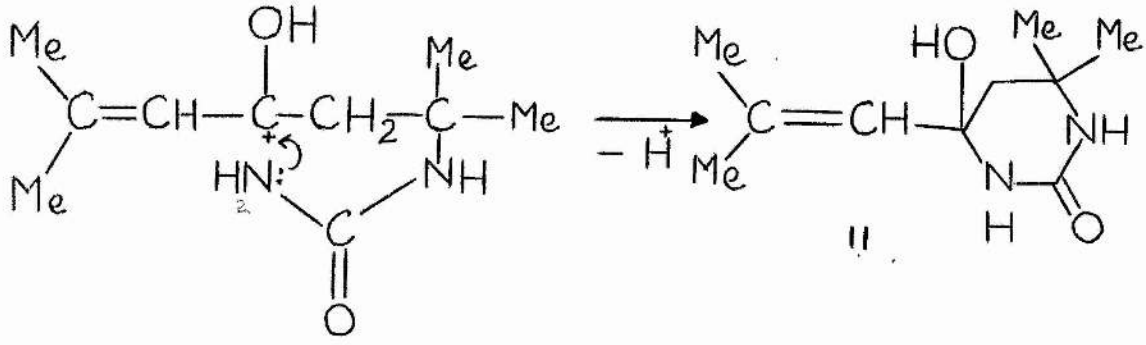

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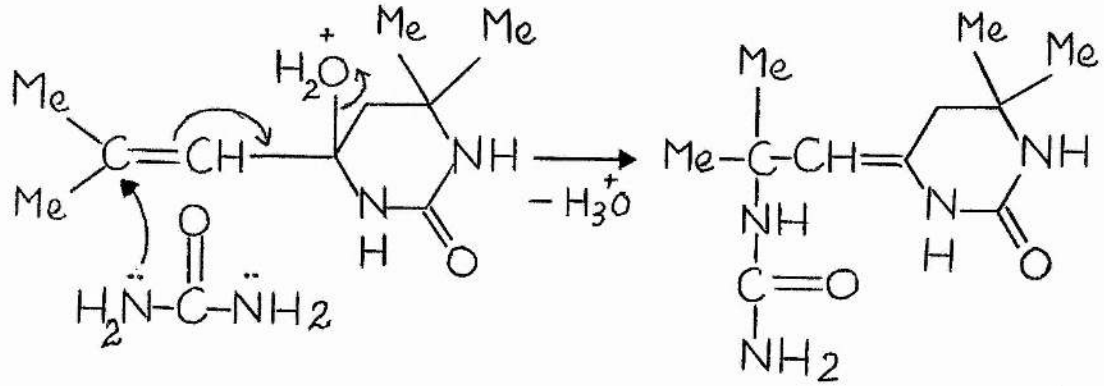

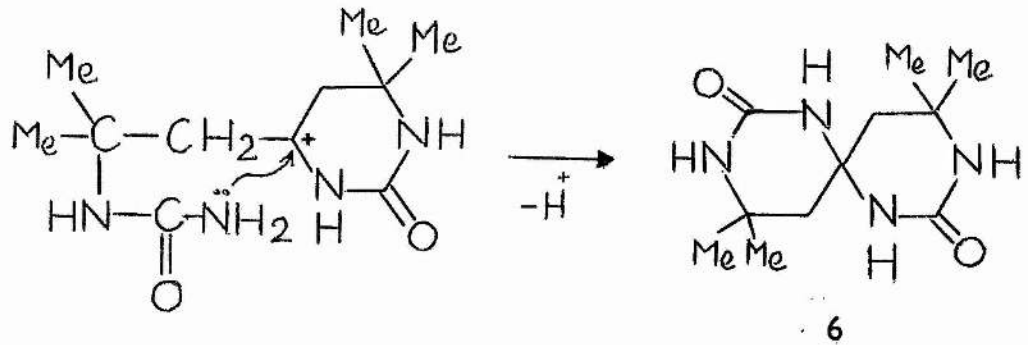

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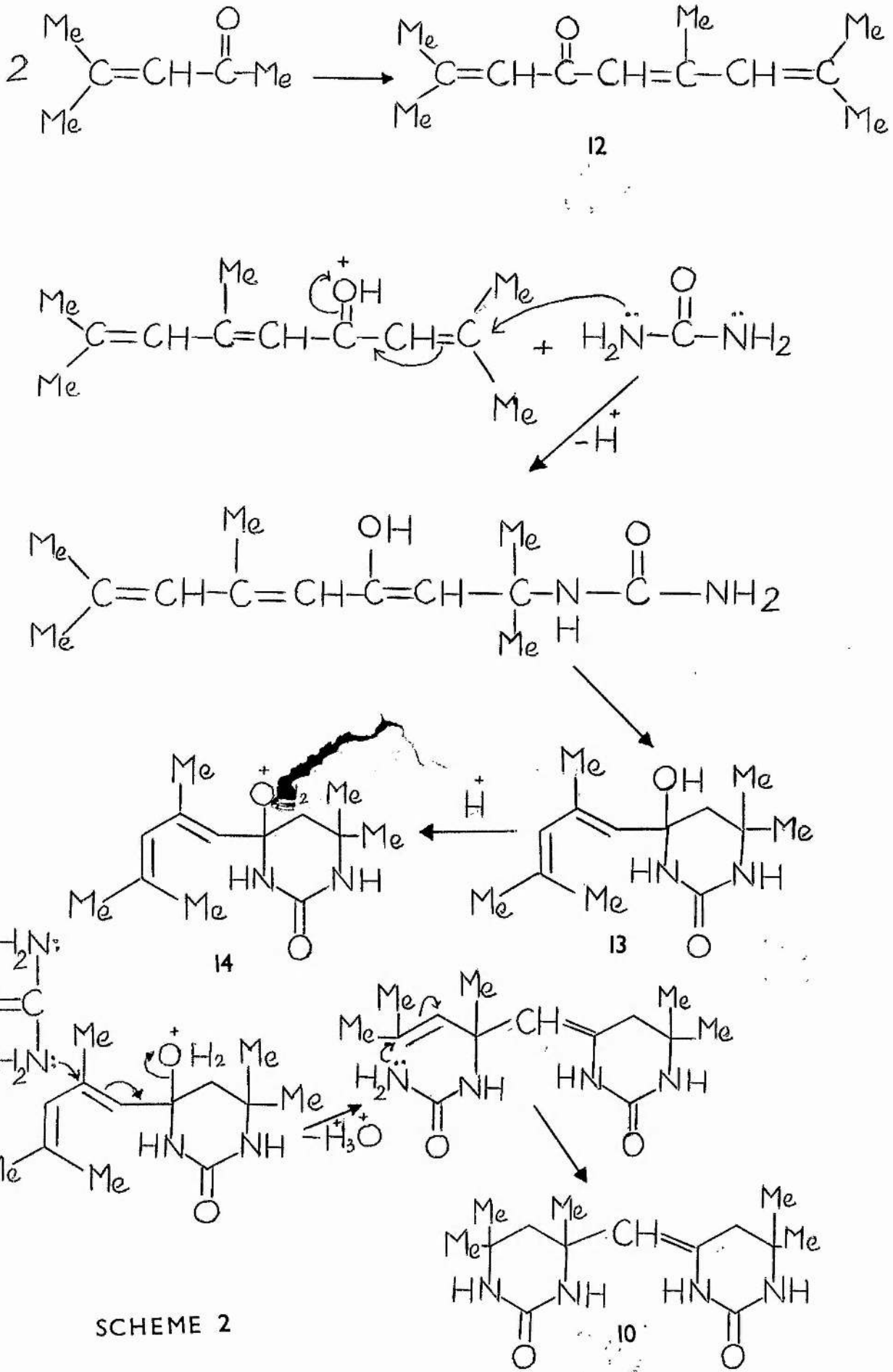
SCHEME I

In the off-resonance spectrum the two peaks assigned to the methylene groups (δ 45.80 and 45.96 ppm) became triplets, one olefinic carbon (δ 114.04 ppm) became a doublet and all the others remained as singlets. The results agree with structure (10).

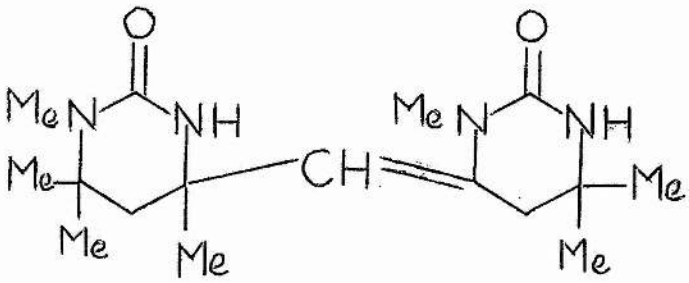
Compound (6) is formed from phorone (7) and urea and this suggests that part of the reaction is the condensation of three molecules of acetone to give (7). Mesityl oxide is probably the first product, but this appears to react faster with a third molecule of acetone than with urea, as (10) is not formed in the reaction between urea and acetone. The mechanism is shown in Scheme 1. Protonation of (7) makes it susceptible to a Michael condensation reaction with urea. If the resulting double bond is protonated then cyclisation can be effected to give (11). Protonation of the hydroxy-group facilitates a second Michael condensation by urea, this time with elimination of water. Protonation of the remaining double bond effects a second cyclisation and formation of the spiro-compound (6).

The reaction with mesityl oxide must follow a different course, although two similar cyclisations occur. The first step appears to be condensation of two molecules of mesityl oxide to form (12). A Michael condensation followed by cyclisation gives (13), which can eliminate water with creation of a double bond. Protonation of the species (13) in succession permits nucleophilic attack by ure and cyclisation to (10). The strange course of the reactions may be due to the low basicity of urea linked with a fair degree of nucleophilicity and the readiness of the intermediates to eliminate the elements of water.



SCHEME 2

15



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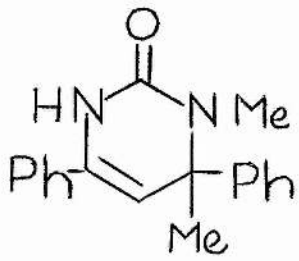


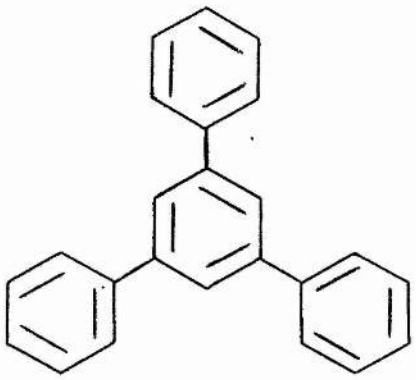
21

Reaction of 1-methylurea with acetone under similar experimental conditions gave an analogous product (15). The structure was elucidated from the proton and carbon-13 nmr spectra. The most diagnostic features of the proton nmr spectrum were three singlets (each of 6H) at δ1.27, 1.36 and 2.72 ppm, generated by the methyl groups, and a distorted double doublet (4H) at 2.22 ppm corresponding to the two methylene groups. There are two variations of (15) with the methyl groups in different relative positions, and we were unable to distinguish between them and thus establish the structure unambiguously. However, if we assume that the mechanism is that shown in Scheme 1, and that the NMe group is the more nucleophilic part of the molecule, then (15) is the resulting product. A side product in this reaction was dimethylcyanuric acid.

The reaction of 1-methylurea with mesityl oxide follows the same course as that of urea and the product is (16). All the spectral data are consistent with this structure. Again there are two other possibilities but one was selected because of the absence of an allylic coupling of the olefinic proton, as had been noted in (21). Unfortunately, the mechanism in Scheme 2 leads to the NMe groups in different relative positions. At present we have no way of fixing the structure unambiguously*.

The only product obtained on the reaction of acetone and 1,3-dimethylurea was 1,3,5-trimethylcyanuric acid.

* see appendix



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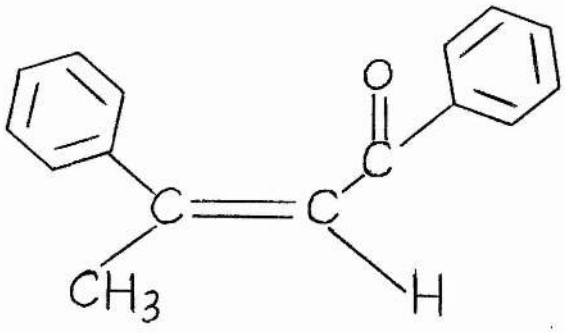
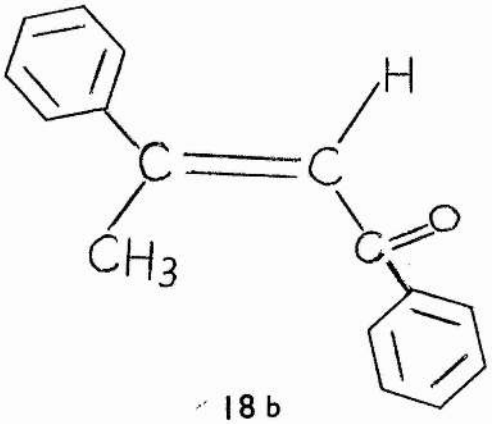


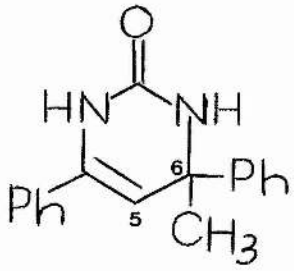
18 a



18 b

Reactions with acetophenone and benzophenone

Equimolar amounts of urea and acetophenone will react with elimination of water, which was removed by azeotropic distillation. Three substances were isolated from the products. Two were the expected self-condensation products of acetophenone, viz. 1,3,5-triphenylbenzene (17) and 1,3-diphenylbut-2-en-1-one (dypnone) (18). The latter is generally prepared by the reaction of acetophenone with aluminium-t-butoxide (Wislicenus, 1895). We have shown, by proton and carbon-13 nmr spectroscopy, that the dypnone we obtained is a mixture of the two isomeric forms (18a and b). The two high field singlets in the proton nmr spectrum (δ 2.42 and 2.54 ppm) show that there are two methyl groups in slightly different environments. There is some evidence of splitting in each of these singlets, due to allylic coupling, but the coupling constants are too small to measure. The total peak area of these two singlets was taken as equivalent to six protons. There is a doublet (δ 7.10 ppm), probably due to the methine proton in (18a), and the peak area indicates one proton. There is another methine proton doublet at lower field (δ 7.89 ppm) but it is too close to the aromatic protons to allow separate determination of the peak area. The complete peak area for the region δ 7.20-7.98 ppm; which includes the methine proton of (18b), corresponds to 21 protons. This is correct for the two phenyl groups of (18a and b) and the methine proton of (18b). The peak areas here, and those for the methyl protons, show that the two isomers are present in equal amounts.



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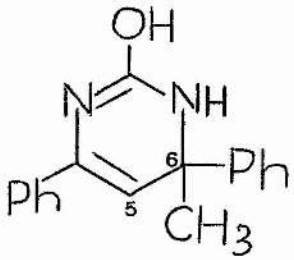


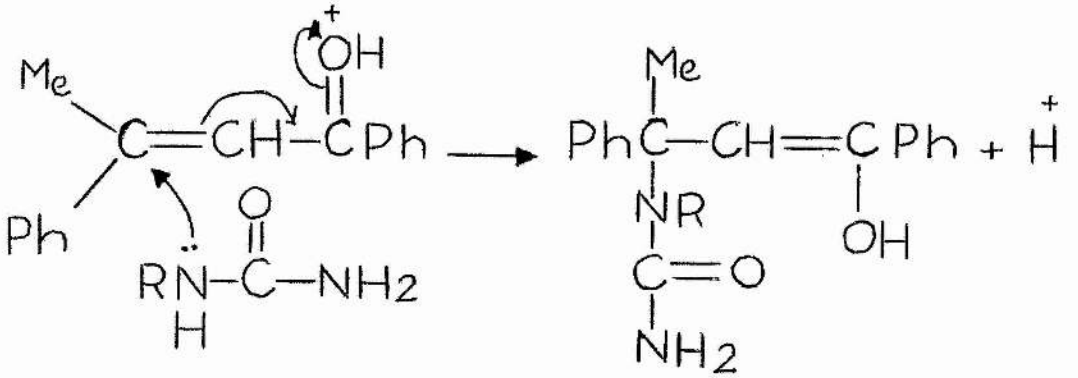
20

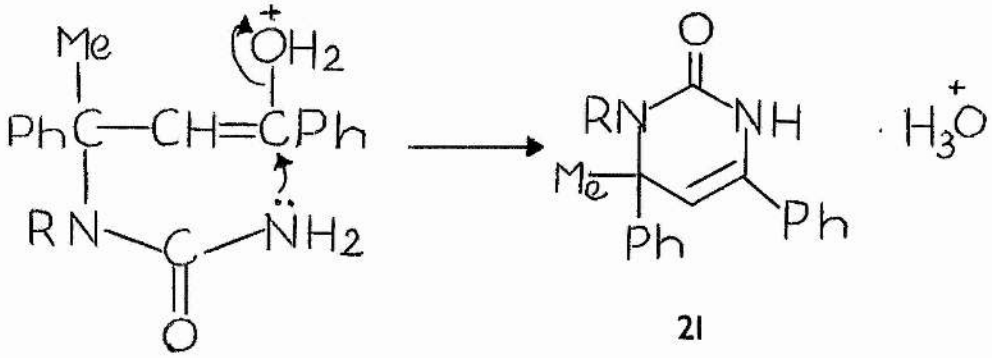
Further evidence for two isomers of dypnone comes from an examination of the carbon-13 nmr spectrum. There again, two shifts corresponding to the two methyl groups (δ17.80 and 25.41 ppm), both of which become quartets in the off-resonance spectrum, and there are two shifts corresponding to two carbonyl groups (δ189.68 and 190.24 ppm).

The third product of reaction is the one of greatest interest to us. This one does contain nitrogen and all the spectroscopic data prove that it is 1,6-dihydro-2-hydroxy-6-methyl-4,6-diphenyl-pyrimidine (19). This compound was first prepared by the reaction of urea and acetophenone by Scholtz (1915) who proposed an open-chain structure. This was questioned by Folkers and Johnson, (1933), who suggested that the product was a reduced pyrimidine. Our evidence supports this assignment. The nomenclature of reduced pyrimidines has been discussed by Brown (1962).

Details of the nmr spectra are given in the Experimental section and only points of special interest will be discussed here. In the proton nmr spectrum only one NH signal is seen (8.66 ppm) suggesting that (19) exists as the hydroxy-compound (20), rather than in the oxo-form. The doublet at 5.35 ppm is of some interest. It is the proton at position 5 split by the NH proton. The splitting disappears on spin tickling. In the carbon-13 nmr spectrum the shifts at δ104.49 and 57.04 ppm are due to C-5 and C-6. The former becomes a doublet in the off-resonance spectrum, while the latter remains as a singlet.

A satisfactory reaction mechanism is one which rationalises

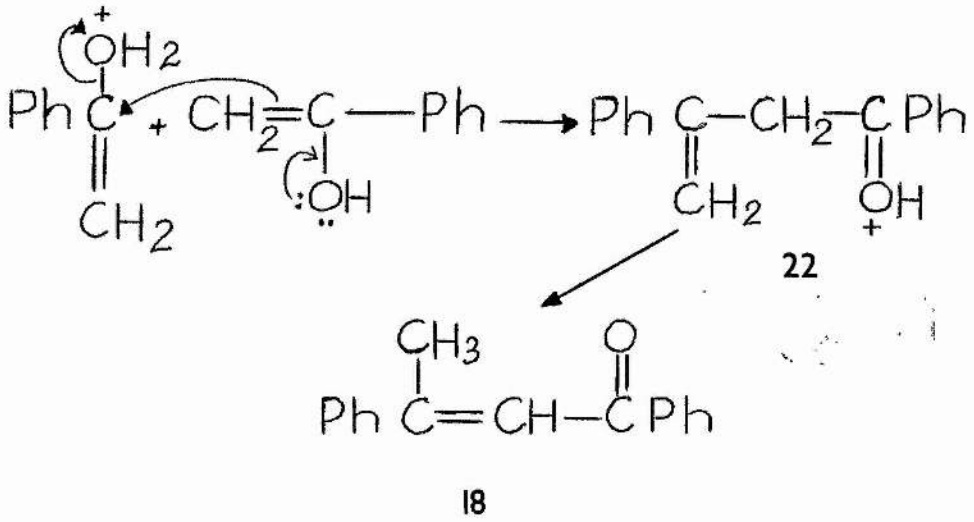




21

$R = CH_3$,

SCHEME 4



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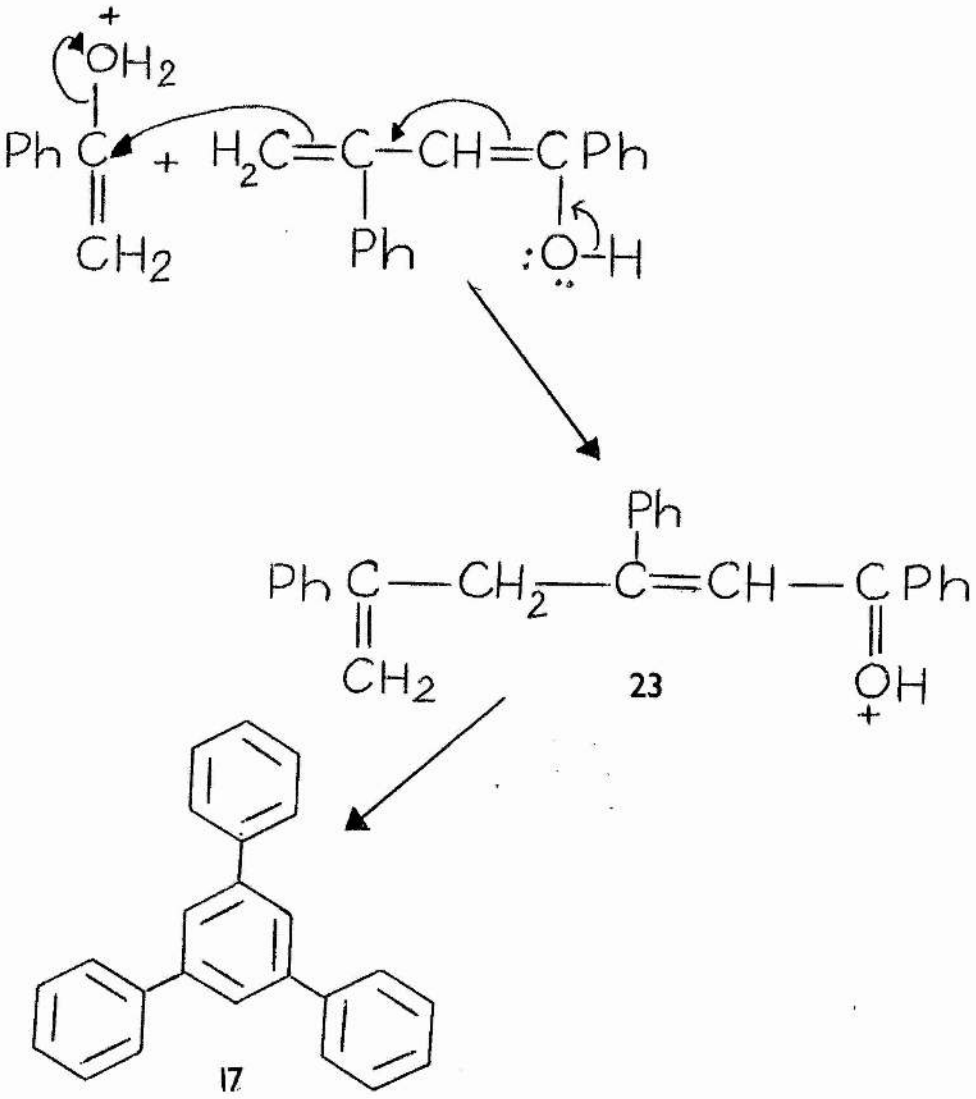


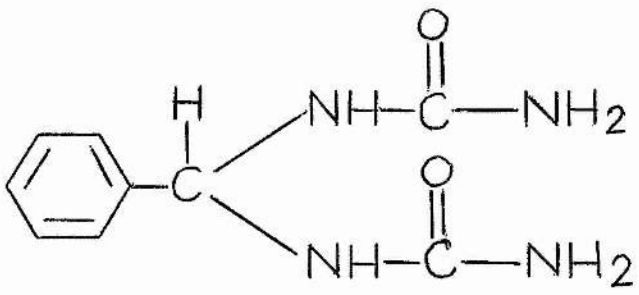
17

SCHEME 3

formation of all three products. Such a mechanism is shown in Schemes 3 and 4. Protonation of the enolic form of acetophenone gives it a good leaving group (water). The unprotonated enolic form of acetophenone can act as a nucleophile and reaction between the two results in the formation of (22), with the elimination of water. Deprotonation and a prototropic shift yields dypnone (18). However, reaction of the enolic form of dypnone with another molecule of protonated acetophenone results in the formation of (23), with elimination of water. Cyclisation of (23) can occur, with elimination of more water and deprotonation, to give triphenylbenzene (17). When urea was omitted from the mixture dypnone was the main product.

However, in the presence of urea dypnone undergoes a reaction other than formation of triphenylbenzene. As shown in Scheme 4, urea may act as a nucleophile and undergo a Michael condensation with dypnone,which is an unsaturated ketone. Protonation of the initial adduct provides a good leaving group (water) for cyclisation to occur.

With 1-methylurea, the main product was (21). All the spectroscopic data are consistent with this structure. The only question is the position of the NMe group relative to the ring double bond. In the proton nmr spectrum the methine hydrogen was split into a doublet and the splitting disappeared on addition of D_2O and on spin tickling. These observations are consistent with structure (21). The structure is right for the mechanism shown in Scheme 4, assuming that the NMe group is the more nucleophilic end of the 1-methylurea molecule.



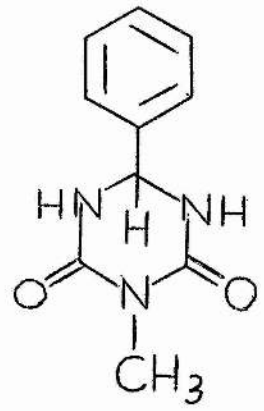
24

With 1,3-dimethylurea, the only product, even after refluxing for 51 h, was dypnone and 1,3,5-triphenylbenzene. The reason for this must be steric. The presence of a methyl group must prevent the cyclisation step shown in Scheme 4 and so there is nothing to drive the reaction towards the stable, cyclic dihydropyrimidine.

Similar reactions to those described above were tried with benzophenone but, in all cases, unchanged starting materials were recovered. This reflects the important role of the methyl group in such reactions.

Reactions with benzaldehyde

The condensation of urea with aliphatic aldehydes has been reported (Ogata et al; 1965, 1966). The products of the reactions are principally alkylidenediureas, although other products are possible. The reaction of urea with benzaldehyde was first reported by Schiff (1869), who suggested an empirical formula for the product of $C_9H_{12}N_4O_2$ and structure (24). Before discussing the reaction of urea with benzaldehyde we thought it would be of interest to examine the reactions of 1-methylurea and biuret with benzaldehyde, because each give a single product. One mole of benzaldehyde and two moles of methylurea react together with elimination of water, to give a crystalline solid which melted sharply at 242°C. Elemental analysis and molecular weight determination suggested a formula of $C_{10}H_{11}N_3O_2$. The proton nmr spectrum in [$^2H_6$] DMSO was, in general, consistent



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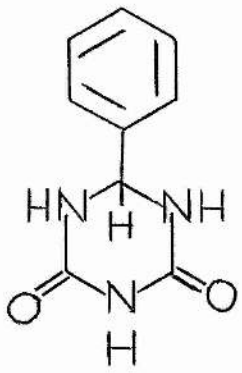
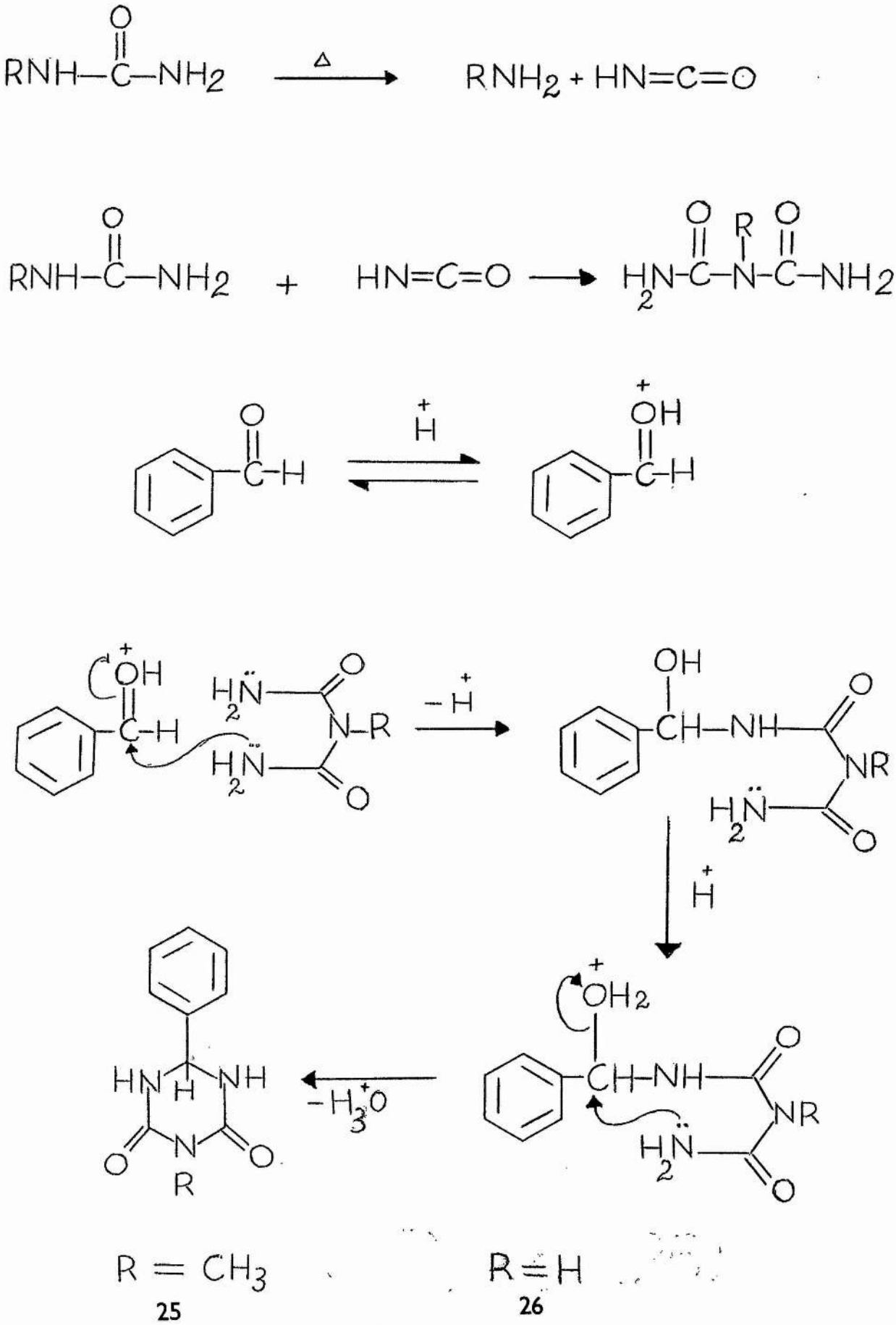


26

with structure (25). Apart from the NMe and aromatic signals at δ 2.95 and 7.45 (5H) ppm, a methine proton shows a triplet centred at δ 5.54 ppm (J 2 Hz) which suggests that it is flanked by two NH protons. The NH protons also exhibit a doublet at δ 8.37 ppm. (2H, J 2Hz). In TFA, this triplet changes into a singlet, suggesting a rapid exchange of NH protons with solvent. The carbon-13 nmr spectrum unequivocally supports (25). The carbonyl groups and a tertiary carbon appear at δ 153.08 and 61.56 ppm; while the remaining carbons resonate at their right places. The ir spectrum is in agreement with the presence of amide carbonyl and NH groups.

Under similar conditions reaction of biuret and benzaldehyde gave a white crystalline product which had m.p. 322-4° (slight dec.). Determination of the nmr spectra was difficult as the compound was insoluble in all the usual solvents. However, in TFA it went into solution with difficulty. The proton and carbon-13 nmr spectra had all the features consistent with structure (26), with some additional peaks which suggested that it had decomposed. The mass spectrum was not clear. It fragmented into pieces and the highest peak that we observed was at m/e=106. Its elemental analysis indicated an empirical formula of $C_9H_9N_3O_2$, and its ir spectrum was consistent with the presence of NH and C=O groups. In the light of all these observations we do not feel any hesitation in suggesting the structure of $C_9H_9N_3O_2$ is (26), analogous to (25).

Similarly, the urea-benzaldehyde reaction gave a white solid which seems to be a mixture. It is insoluble in all regular solvents and difficult to purify. However, physical, chemical



R = CH3 (25) R = H (26)

SCHEME 5

and spectroscopic evidence reflect that it is (26) with some unidentified material. A reaction mechanism relating to these products is shown in Scheme 5. Urea on heating changes to biuret, which reacts with benzaldehyde in an acid media to yield (26). Moreover, reaction with pure biuret supports this view.

EXPERIMENTAL

Preparation of products from acetone and mesityl oxide

a) 4,4'-Spirobi-6,6-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1H)one (6)

Urea - A mixture of urea (6 g) and acetone (8.5 ml) in benzene (50 ml) in the presence of TFA (5 ml) was refluxed for 7 h at 90°. An azeotropic distillation technique was used to separate the water formed during the reaction. On cooling, a white solid and a yellowish liquid were obtained. Benzene was removed by decantation and material was dissolved in hot ethanol. White crystals appeared on cooling and were recrystallised from hot water. When dried, the solid had m.p. 265° (dec.) (lit. 265°, Weinschenk, 1901). The same technique was used in all experiments.

b) Spiro-compound (15)

1-Methylurea - A mixture of acetone (10 ml) and methylurea (7.4 g) in benzene (50 ml) and TFA (5 ml) was refluxed for 4 h at 90°. After removal of benzene the residue was purified by column chromatography (Al_2O_3). The material was eluted with $CHCl_3$ and recrystallised from $CHCl_3$, m.p. 328°.

c) 6,6-Dimethyl-4-(4,6,6-trimethyl-2-oxoperhydropyrimidine-4-ylmethyl)-3,6-dihydropyrimidin-2(1H)-one (10)

Urea - Mesityloxide (13 ml), urea (6 g) in benzene (50 ml) and TFA (5 ml) were refluxed for 4 h at 90°. After chromatography the product was recrystallised from methanol, m.p. 302° (lit. 295°, Zigeuner et al; 1966).

d) Pyrimidinylmethylpyrimidone (16)

1-Methylurea - After removal of the benzene the residue was purified by column chromatography (Al_2O_3). The product was eluted with $CHCl_3$ and recrystallised from acetone, m.p. 202°.

Reaction products from acetophenone

e) Urea - Urea (0.1 mol), acetophenone (0.1 mol), benzene (50 ml) and TFA (5 ml) were refluxed for 11 h. The benzene was decanted to leave a red gum. Most of the gum dissolved in methanol but there remained some crystals of triphenylbenzene (17) which was recrystallised from acetone, m.p. 172° (lit. 174°, Folkers and Johnson, 1933).

The methanol was removed and the residue was put onto an alumina column. The column was eluted with ether and then with methanol. Removal of the ether gave a yellow liquid, which was 2-benzoyl-1-methyl-1-phenylethylene (18).

Solvent was removed from the methanol eluant to give a solid, 4-methyl-4,6-diphenyldihydropyrimidin-2-one (19), m.p. 170°.

f) 1-Methylurea - The above procedure was repeated using 1-methylurea and refluxing for 20 h. After removal of the benzene a yellow oil remained which solidified on standing. Crystals of 3,4-dimethyl-4,6-diphenylpyrimidin-2-one (21) was recrystallised from ethanol, m.p. 193°.

Reaction products from benzaldehyde

g) Urea - A mixture of benzaldehyde (0.2 mole) and urea (0.1 mol) in benzene (50 ml) containing TFA (5 ml) was refluxed for 6 h with removal of water as described above. On cooling, a white solid settled down. Excess acetone was added and filtered off the white substance, washed with water, acetone and finally with ether, dried, m.p. 260° (not sharp).

h) Biuret - The above procedure was repeated. A white solid was collected, m.p. 324° (dec.) (26) 4-phenyl-1,3,5-triazine-2,6-dione.

i) 1-Methylurea - The reaction product was filtered off, washed with ether, water, dissolved in a minimum amount of DMSO and brought out crystals by addition of water. Dried, m.p. 242° 4-phenyl-1-methyl-1,3,5-triazine-2,6-dione (25)

Physical Data

a) 4,4'-Spirobi-6,6-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1H)-one (6)

M.p. 265° (lit, 265°, Weinschenk, 1901), m/e 240 ($M^+ - H_2O$), ν_{max} 3510, 3340, and 3215 (NH) and 1660 cm^{-1} (C=O); δH ([$^2H_6$]DMSO, 120°) 1.15, 1.18 (12H, 2s), 1.89 (4H, dd, J_{gem} 14 Hz), and 5.88, 5.99 (4H, 2s) ppm, δC 30.22, 48.01, 52.98, 68.32 and 158.63 ppm. (Found: C, 51.15; H, 8.4; N, 22.4. $C_{11}H_{22}N_4O_3$ requires C, 51.15; H, 8.6; N, 21.7%).

b) Spiro-compound (15)

M.p. 328°, m/e 268 (M^+), ν_{max} 3290 (NH), 1670, and 1655 cm^{-1} (C=O); δH ($CDCl_3$) 1.27 (6H, s), 1.36 (6H, s), 2.22 (4H, dd, J_{gem} 14 Hz), 2.72 (6H, s) and 5.14 (2H, s) ppm; δC 18.44, 27.74, 28.81, 31.72, 44.23, 48.37, 58.24 and 156.86 ppm (Found: C, 57.85; H, 8.85; N, 20.90. $C_{13}H_{24}N_4O_2$ requires C, 58.18; H, 9.01;, N, 20.87%).

c) 6,6-Dimethyl-4-(4,6,6-trimethyl-2-oxoperhydropyrimidin-4-ylmethyl)-3,6-dihydropyrimidin-2(1H)-one (10)

M.p. 302° (lit. 295°, Zigeuner et al; 1966); m/e 280 (M^+), ν_{max} 3428 and 3220 (NH), 1695 (C=O), and 1670 cm^{-1} (C=C); δH (CF_3CO_2H) 1.45, 1.49, 1.59 (15H, 3s), 2.04 (2H, dd, J_{gem} 14 Hz), 2.56 (2H, dd, J_{gem} 14 Hz), 4.86 (1H, s), 7.08 (1H, s), and 8.26 (1H, s) ppm, δC (CF_3CO_2H) 28.44, 30.62, 31.08, 31.57, 45.80, 45.96, 53.65, 55.70, 56.48, 114.04, 128.73, 158.20 and 158.47 ppm (Found: C, 59.45; H, 8.65; N 19.85. $C_{14}H_{24}N_4O_2$ requires C, 59.97; H, 8.62; N, 19.98%).

d) Pyrimidinylmethylpyrimidone (16)

M.p. 202°; m/e 308 (M^+); ν_{max} 3210 (NH), 1680, 1660 (C=O) and 1630 cm^{-1} (C=C); δH ($CDCl_3$) 1.23 (9H, s), 1.31 (3H, s), 1.53 (3H, s), 2.02 (2H, dd, J_{gem} 14 Hz), 2.47 (2H, dd, J_{gem} 14 Hz), 2.85 (3H, s), 3.13 (3H, s), 4.77 (1H, s), 5.82 (1H, s) and 6.66 (1H, s) ppm, δC 28.27, 28.51, 28.81, 29.62, 30.28, 30.43, 31.69, 35.99, 48.05, 48.79, 56.69, 112.22, 137.36, 153.56 and 156.21 ppm (Found: C, 61.55; H, 9.45; N, 18.60. $C_{16}H_{28}N_4O_2$ requires C, 62.3; H, 9.15; N, 18.15%).

e) 1,3,5-Triphenylbenzene (17)

M.p. 172° (lit. 174°, Folkers and Johnson, 1933), m/e 306 (M^+); δH ($CDCl_3$) 7.10-7.75 (m) ppm, δC ($CDCl_3$) 125.19, 127.39, 127.54, 128.86, 141.23, and 142.40 ppm λ^{CHCl_3} 255 nm (lit. λ^{CHCl_3} 252 nm).

2-Benzoyl-1-methyl-1-phenyl-ethylene (18)

m/e 222 (M^+), ν_{max} 1690 and 1660 (C=O) and 1600 cm^{-1} (C=C); δH ($CDCl_3$) 2.42 (3H, s), 2.54 (3H, s), 7.10 (1H, d, J 2 Hz), and 7.20-7.98 (21H, m) ppm, δC 17.80, 25.41, 121.06, 125.69, 126.51, 127.43, 127.73, 128.06, 128.33, 131.60, 132.05, 136.36, 138.64, 141.77, 153.75, 189.68, and 190.24 ppm.

4-Methyl-4,6-diphenyldihydropyrimidin-2-one (19)

M.p. 170°, m/e 264 (M^+); ν_{max} (mull) 3240 (NH), 1690 (C=O), and 1650 cm^{-1} (C=C); δH ([$^2H_6$]DMSO) 1.62 (3H, s), 5.35 (1H, d, J 2 Hz), 7.18-7.55 (10H, m), and 8.66 (1H, s) ppm, δC ([$^2H_6$]DMSO)

30.80, 57.04, 104.49, 124.79, 125.38, 126.35, 128.11, 128.29, 134.04, 148.78, and 153.86 ppm (Found: C, 77.1; H, 6.1; N, 10.6. $C_{17}H_{16}N_2O$ requires C, 77.25; H, 6.1; N, 10.6%).

f) 3,4-Dimethyl-4,6-diphenylpyrimidin-2-one (21)

M.p. 193°, m/e 278 (M^+), ν_{max} (mull) 3200 (NH), 1680 (C=O), and 1665 cm^{-1} (C=C), δH ($CDCl_3$) 1.68 (3H, s), 2.86 (3H, s), 5.00 (1H, d, J 2Hz), 5.90 (1H, s) and 7.20-7.50 (10H, m) ppm. δC ($CDCl_3$) 30.93, 32.26, 56.68, 109.91, 124.84-129.29, 135.53, 139.30, 147.80, and 155.54 ppm (Found: C 77.75; H 6.65; N, 10.2 $C_{18}H_{18}N_2O$ requires C, 77.65; H, 6.5; N 10.05%).

g) Compound obtained from the reaction of urea with benzaldehyde

M.p. 260° (not sharp), ν_{max} (mull) 3320 (NH) and 1650 cm^{-1} (C=O); δH (CF_3CO_2H) 6.0 (s), 7.4-8.2 (m), 9.85 (s) ppm integration is not clear, δC (CF_3CO_2H) 67.47, 131.00, 132.72, 138.56 and 171.98, and additional peaks at 128.13, 136.65 ppm suggest that it decomposes in TFA.

h) 4-Phenyl-1,3,5-triazine-2,6-dione (26)

M.p. 323°, ν_{max} 3300 (NH) and 1680 cm^{-1} (C=O), δH (CF_3CO_2H) 5.98 (1H, s), 7.44 (5H, m), 9.90 (1H, s) ppm, δC 67.33, 130.89, 131.14, 132.62, 138.32 and 172.07 ppm. A few other additional peaks suggest that it decomposes in TFA. (Found: C, 56.69; H, 4.94; N, 20.06 . $C_9H_9N_3O_2$ requires C, 56.54; H, 4.74; N, 21.97%).

i) 4-Phenyl-1-methyl-1, 3, 5-triazine, 2, 6-dione (25)

M.p. 242°, m/e 204 (M^+–H); ν_{max} 3320-3260 (NH) and 1680 cm^{-1} (C=O), δH ([$^2H_6$]DMSO) 2.95 (3H, s), 5.59 (1H, t, J 2 Hz), 7.42 (5H, s), 8.37 (2H, d, J 2 Hz) ppm, δC 26.73, 61.56, 126.23, 128.43, 128.62, 141.08 and 153.08 ppm. (Found: C, 58.53; H, 5.29; N, 20.65. $C_{10}H_{11}N_3O_2$ requires C, 58.52; H, 5.40; N, 20.47%).

CHAPTER 2

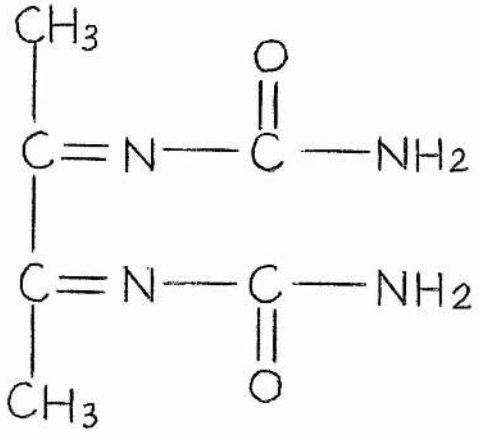
Reaction of urea, 1-methylurea, 1,3-dimethylurea and ethyleneurea with butane-2,3-dione, 1-phenylpropane-1,2-dione, some acyloins, and cyclohexane-1,2-dione.

INTRODUCTION

Unlike monoketones, α-diketones containing at least one methyl group adjacent to a carbonyl group react readily with urea and its N-alkyl derivatives, in acid solution, to give intensely coloured products. These colours have been used by Ormsby (1942), Dickenman et al (1954) and Siest (1967) for the determination of urea concentrations in biological fluids. Of the three α-diketones, butane-2,3-dione has been extensively used and is often preferred to the urease method, while 1-phenylpropane-1,2-dione and cyclohexane-1,2-dione have never been widely used in hospital laboratories.

The urease method (Woottom, 1974; Henry et al, 1974; and Jung et al, 1975) is an indirect method involving the measurement of ammonia liberated as a result of the action of the enzyme urease, found in moulds, bacteria and plants (e.g. Jack bean), on urea. Disadvantages in the urease method arises from the fact that other ammonia may already be present in the sample and this needs to be measured, from urease inhibition or inactivation, and from reagent instability.

Butane-2,3-dione, by contrast, does not measure ammonia, uses stable reagents, and is quite sensitive and specific. Its main disadvantages are that the colour is photosensitive, unstable and requires development at the temperature of boiling water, and that the time for colour development is dependent on the urea concentration. If the monoxime of butane-2,3-dione is used, the presence of an oxidising agent, such as potassium persulphate, is required to destroy any hydroxylamine formed. Thiosemicarbazide is often added to



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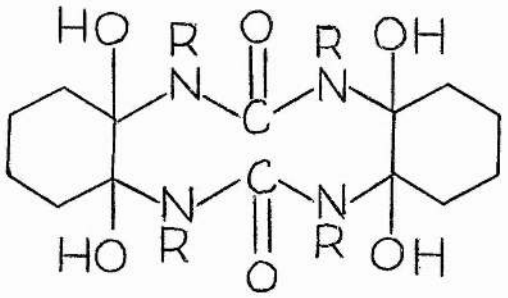

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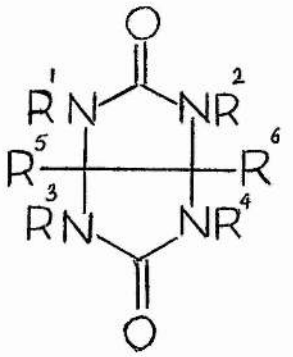


28

a $R^1 = R^2 = R^3 = R^4 = H,\ R^5 = R^6 = Me$

b $R^1 = R^2 = R^3 = R^4 = H,\ R^5 = Ph,\ R^6 = Me$

c $R^1 = R^4 = Me,\ R^2 = R^3 = H,\ R^5 = R^6 = Me$

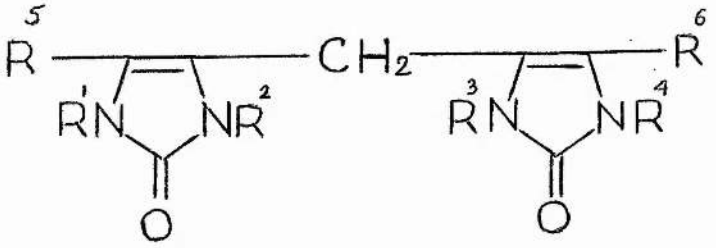
d $R^1 = R^3 = Me,\ R^2 = R^4 = H,\ R^5 = R^6 = Me$

e $R^1 = R^4 = Me,\ R^2 = R^3 = H,\ R^5 = Ph,\ R^6 = Me$

f $R^1 = R^3 = Me,\ R^2 = R^4 = H,\ R^5 = Ph,\ R^6 = Me$

g $R^1 = R^2 = R^3 = R^4 = H,\ R^5 = R^6 = Ph$

h $R^1 = R^3 = H,\ R^2 = R^4 = Me,\ R^5 = R^6 = Ph$



33

a $R^1 = R^4 = Me,\ R^2 = R^3 = H,\ R^5 = R^6 = Ph$

d $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = Me$

h $R^1 = R^2 = R^3 = R^4 = H,\ R^5 = R^6 = Ph$

intensify the colour and to minimise photosensitivity, while the presence of certain cations such as ferric ions help to stabilise the colour.

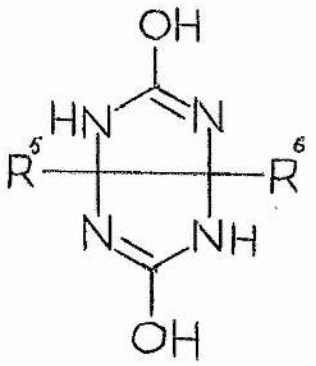
This work looks into the reaction of butane-2, 3-dione, 1-phenylpropane-1, 2-dione, some acyloins and cylohexane-1, 2-dione with urea, 1-methylurea, 1, 3-dimethylurea, and finally with ethyleneurea, in order to elucidate the reaction mechanisms and to identify the substances responsible for the colours that form. The chromogen that we obtained from the reaction of diacetyl and 1, 3-dimethylurea is (33d) and its structure has been confirmed by an X-ray crystallographic method (Glidewell and Holden, 1980). Similar products (33a, 33h) that are responsible for colours were also isolated from the reaction of butane-2, 3-dione and 1-phenylpropane-1, 2-dione with urea and methylurea in addition to bicyclic compounds (28a-h). These bicyclic compounds continue to react in the presence of acid to produce highly coloured species. The reaction of cyclohexane-1, 2-dione with ureas yields another kind of chromophore which is (55).

Finally, we have observed that the colour formation depends upon the strength of the acid and boiling time, not on the presence of ions (e.g. Fe^{3+}, Fe^{2+}, PO_4^{3-}, Cl^-) and thiosemicarbazide. Once the colour is fully developed, it remains insensitive to light.

RESULTS AND DISCUSSION

Reaction of urea with butane-2, 3-dione in acid solution gave a white crystalline material of molecular formula $C_6H_{10}N_4O_2$. Lugosi et al (1972) suggested structure (27) for this material but there is evidence against this. It was difficult to obtain spectral data for the product as it is insoluble in the usual organic solvents. However, it does dissolve in TFA and the material may be recovered unchanged from this solvent. In its proton nmr spectrum there are two singlets at δ 1.80 (6H) and 7.3 (2H) ppm. Two protons belonging to nitrogen atoms are missing, which reflects that rapid exchange of NH occurs. In the carbon-13 nmr spectrum there is only one resonance at low field (the carbonyl) but (27) requires a second due to the C=N group. There is, however, a tertiary carbon at δ 80.6 ppm. These data are consistent with (28a). Other spectral data are in agreement with this structure.

Similarly, a crystalline product was obtained from the reaction of 1-phenylpropane-1,2-dione and urea. Molecular weight determination and elemental analysis gave a molecular formula of $C_{11}H_{12}N_4O_2$, which corresponds to reaction of one mole of the dione with two moles of urea and elimination of two moles of water. This immediately suggested 3a-methyl-7a-phenyltetrahydro-imidazo[4,5-d]imidazole-2,5-dione (28b) as the structure of the product. The ir spectrum is consistent with the presence of amide carbonyl groups, NH groups, and the absence of C=N. Determination of the nmr spectra was difficult as the compound was insoluble in all the usual solvents. However, it was soluble enough in $[^2H_6]$DMSO



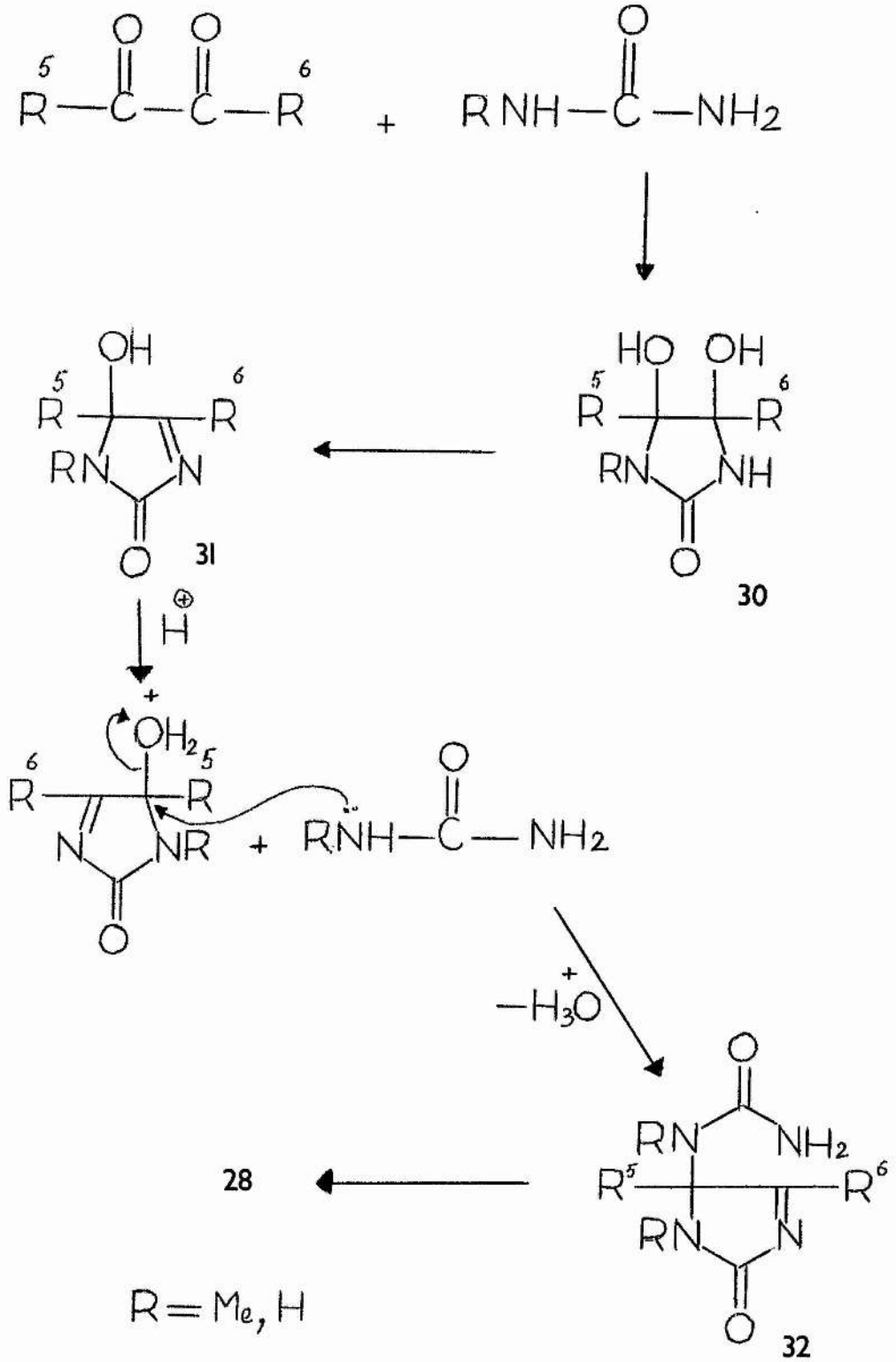
29

a $\overset{5}{R}=\overset{6}{R}=Me$

b $\overset{5}{R}=Ph,\ \overset{6}{R}=Me$

at 110° to allow measurement of the proton nmr spectrum. This had four singlets with relative peak areas 3:1:1:5. The first and the last are clearly due to the methyl and the phenyl groups, while the others, at δ 6.61 and 6.93 ppm, are due to two of the remaining protons. The fact that only two out of the four remaining are observable suggests that exchange is occurring. The compound may, of course, exist in the tautomeric form (29b). The only suitable solvent for measurement of the carbon-13 nmr spectrum was TFA. Such a strong acidic substance is obviously not the solvent of choice but, when the solvent was removed after the spectrum had been obtained, the material was recovered unchanged. We have, therefore, confidence that the results obtained do correspond to the carbon skeleton of the product. There were five shifts as well as a group at δ 127.79-135.31 ppm corresponding to the carbons of the phenyl group. The two at lowest field, δ 164.93 and 164.64 ppm, indicate that the two carbonyl groups are in slightly different magnetic environments. Of the others, two (δ 82.37 and 85.07 ppm) remained as singlets in an off-resonance spectrum, which is right from the two tertiary carbons common to both rings. The shift at highest field (δ 23.96 ppm) became a quartet in the off-resonance spectrum, which is right for a methyl group. The carbon-13 nmr spectrum is, therefore, entirely consistent with structure (28b).

With 1-methylurea, butane-2,3-dione yielded a white crystalline solid, of formula $C_8H_{14}N_4O_2$. The same product was obtained by reaction in ethanol saturated with HCl. This compound results from the reaction of two molecules of 1-methylurea with one molecule of the dione and elimination of two molecules of water.

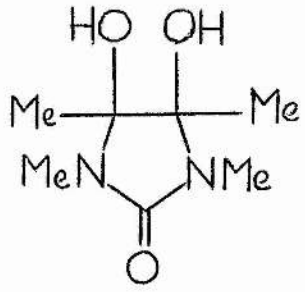

R⁵—C(=O)—C(=O)—R⁶ + RNH—C(=O)—NH₂
HO OH
R⁵ R⁶
RN NH
O
30
OH
R⁵ R⁶
RN N
O
31
H⊕
OH₂
R⁶ R⁵
N NR
RNH—C(=O)—NH₂
−H₃O⊕
RN NH₂
R⁵ R⁶
RN N
O
32
28
R = Me, H

SCHEME 6

The ir spectrum indicated the presence of NH and carbonyl groups. The proton nmr was rather complex with seven singlets. These we ascribe to three methyl groups, two N-methyl groups and two NH groups. The spectrum could indicate an unsymmetrical molecule or a mixture of isomers. We propose the latter: (28c) and (28d). In (28c) the two methyl groups are identical but in (28d) they differ. Each contains only one type of N-methyl and NH group. These structures were confirmed by the carbon-13 nmr spectrum of the product. There is evidence for two different carbonyl (one in each isomer) and five peaks in the range δ 16.23-28.00 ppm corresponding to the five different methyl groups. There were three different tertiary carbons (the peaks remained as singlets in the off-resonance spectrum) at δ 78.56, 82.34, and 86.62 ppm, one in (28c) and two in (28d).

We propose a mechanism for the formation of (28a-d) in Scheme 6 which is similar to that suggested for the reaction of 1-methylurea with benzil (Butler and Leitch, 1980). The crucial intermediate is (31) formed by elimination of water in acid conditions from the diol (30). If (31) is protonated on the hydroxyl group a good leaving group (water) is formed and displacement by a second 1-methylurea molecule forms (32). Ring closure occurs by addition across the carbon-nitrogen double bond, probably by N-protonation and generation of a carbonium ion, which reacts with the nucleophilic $-NH_2$ group. Attack of protonated (31) by the other end of the 1-methylurea molecule gives (28c), rather than (28d), and so the mixture of isomers is explained.

The intermediacy of (31) explains why 1,3-dimethylurea does



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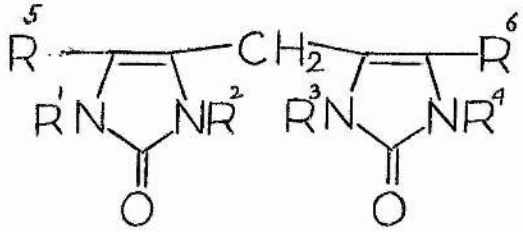


33

a $R^1 = R^4 = Me,\ R^2 = R^3 = H,\ R^5 = R^6 = Ph$

b $R^1 = R^4 = H,\ R^2 = R^3 = Me,\ R^5 = R^6 = Ph$

c $R^1 = R^3 = Me,\ R^2 = R^4 = H,\ R^5 = R^6 = Ph$

d $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = Me$

e $R^1 = R^4 = Me,\ R^2 = R^3 = H,\ R^5 = R^6 = Me$

e' $R^2 = R^3 = Me\ \ R^1 = R^4 = H,\ R^5 = R^6 = Me$

f $R^1 = R^2 = R^3 = R^4 = H,\ R^5 = R^6 = Me$

g $R^1 = R^2 = R^3 = R^4 = Me,\ R^5 = R^6 = Ph$

h $R^1 = R^2 = R^3 = R^4 = H,\ R^5 = R^6 = Ph$

not form a product analogous to (28). The diol (37) cannot eliminate water to give a double bond in the ring. Thus, this reaction pathway is blocked and an entirely different one gives (33d) as the main product. A similar effect was noted in the reaction of 1,3-dimethylurea with benzil (Butler and Leitch, 1980) and with 1-phenylpropane-1,2-dione (see later). With the former a hydantoin formed, while the latter gave a spiro-compound. With urea products (28a) and (28b) were obtained.

1-Phenylpropane-1,2-dione does not react with 1-methylurea in the same manner as butane-2,3-dione. The product obtained is (33a-c) rather than bicylic compounds (28e-f). After removal of the benzene and chromatography of the residue, crystals were obtained. Elemental analysis indicated a formula of $C_{21}H_{20}N_4O_2$ and this was confirmed by the mass spectrum. This formula corresponds to reaction of two moles of dione and two moles of methylurea, with loss of four moles of water and one carbon atom. During the azeotropic distillation evolution of carbon dioxide was detected by passing the vapours through baryta water. The ir spectrum suggested the presence of NH, C=O, and C=C groupings. A methanolic solution of the material decolorised neutral potassium permanganate, which also suggests a carbon-carbon double bond. Neither 1-phenylpropane-1,2-dione, nor 1-methylurea react in the same way.

It was interesting to find that a similar product was obtained by Kuono and Ueda (1971) on reaction of 1-butylurea with 1-phenylpropane-1,2-dione and glucoronolactone in aqueous

phosphoric acid. The molecular formula of their product was $C_{27}H_{32}N_4O_2$ which is condensation of two molecules of the dione with two molecules of 1-butylurea and loss of four moles of water and one of carbon.

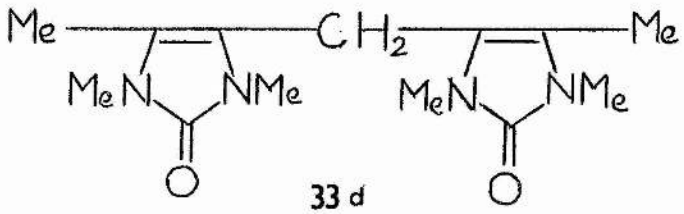
The proton nmr spectrum of our compound at 100 MHz in [$^2H_6$]DMSO was very simple: three singlets with relative peak areas 6:2:12 at δ 2.82, 4.04 and 7.30 ppm, respectively. We assign these to two N-methyl groups, a methylene in a carbon skeleton, two phenyl groups overlapping with two broad peaks due to NH.

The carbon-13 nmr spectrum was equally simple: peaks corresponding to the carbonyl groups, the phenyl carbons, and the N-methyl groups and three others at δ20.31, 115.46 and 118.77 ppm. In the off-resonance spectrum the first became a triplet, while the other two remained as singlets. The second and third shifts are right for an unsymmetrical C=C group, while the first must be due to a methylene groups.

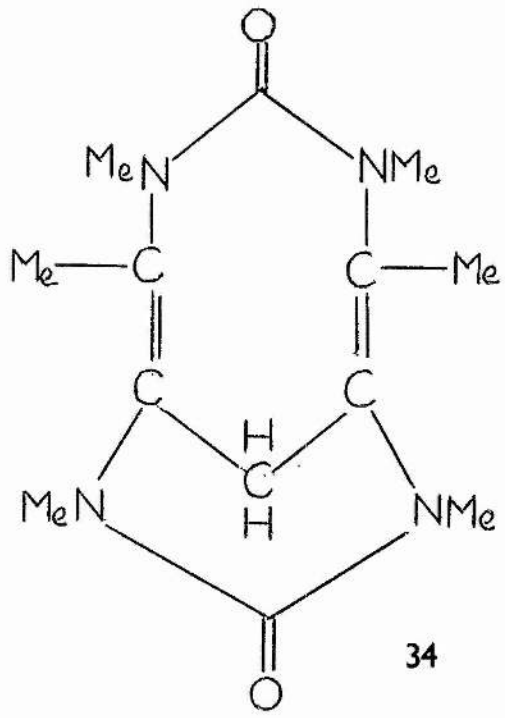
However, despite all these facts, it is difficult to be certain about the relative positions of the two N-methyl groups. There are three possibilities (33a), (33b) and (33c). In the 360 MHz proton nmr spectrum two different N-methyl groups are indicated with δ 1.19 and 1.50 ppm. This could mean (33c) or a mixture of (33a) and (33b). As the integrals for the two peaks are different, (33c) is not possible and we must have a mixture containing unequal amounts of (33a) and (33b). This is confirmed by two unequal peaks at δ 3.01 and 3.13 ppm, corresponding to two different methylene groups.

Before discussing the reaction mechanism pertaining to formation of (33a) and (33b), we now come to consider the reaction of 1,3-dimethylurea with butane-2,3-dione, because they yield a product of similar carbon skeleton. Refluxing the reactants in benzene and TFA resulted in formation of water and a purple solution. Removal of solvent left a viscous mass, which was purified by column chromatography to yield white crystals. This material has a molecular formula of $C_{13}H_{20}N_4O_2$ and must be formed from the condensation of two molecules of 1,3-dimethylurea and two molecules of butane-2,3-dione with elimination of four molecules of water and one carbon atom.

The ir spectrum of the product suggested the presence of carbonyl groups and carbon-carbon double bonds. The 360 MHz proton nmr spectrum was unexpectedly simple: two pairs of N-methyl groups (δ 2.89 and 2.81 ppm), two identical methyl groups (δ 1.68 ppm) and a methylene group at low field (δ 3.25 ppm). This gives the correct total of 20 protons. The carbon-13 nmr spectrum was equally simple, with only six resonances; this suggested a symmetrical molecule. Apart from the peaks assigned to the methyl groups, the N-methyl groups, and the carbonyl groups, there are two others at δ 112.60 and 115.03 ppm. These are correct for carbons of unsymmetrical double bond. The remaining resonance was at δ 19.00 ppm, and in the off-resonance spectrum, became a triplet and was identified as that due to the methylene group. As the peak in the proton nmr spectrum is not split by geminal coupling, the methylene groups appears not to be part of a ring.



33 d



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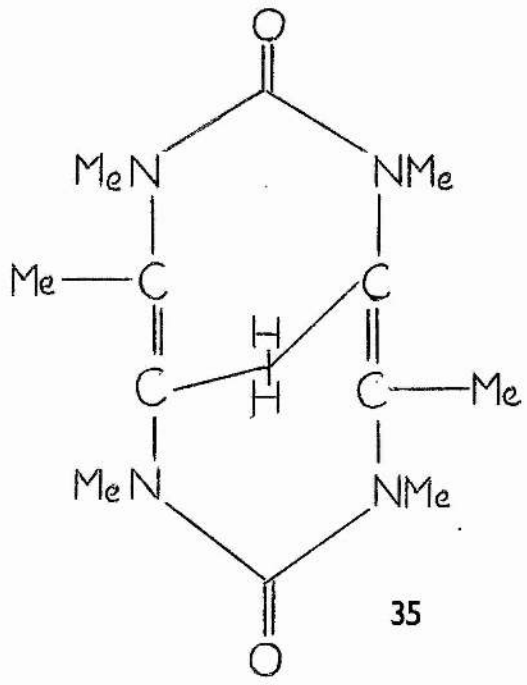

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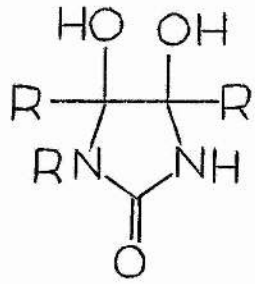
There are three structures (33d), (34) and (35) of different degrees of credibility, which are consistent with the spectral data. Fortunately discussion of their relative merits can be avoided as we have an X-ray crystal structure of the product (Glidewell and Holden, 1980). It is 4,4'-methylenebis-(1,3,5-trimethyl-4-imidazolin-2-one) (33d). This molecule has all the features deduced from the spectral data: two pairs of N-methyl groups, two identical methyl groups, two unsymmetrical carbon-carbon double bonds, two identical carbonyl groups, and a single methylene group. It is also symmetrical.

We now come to propose a reaction mechanism for the formation of (33d) from butane-2,3-dione and 1,3-dimethylurea. The first problem is the fate of missing carbon. Evolution of carbon dioxide was detected during the course of the azeotropic distillation but this could have resulted from elimination of formaldehyde, oxidation of formic acid and decomposition at the temperature of refluxing benzene.

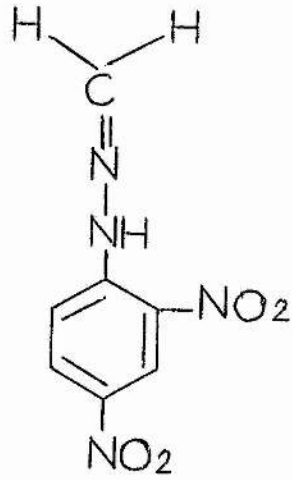
Reaction between butane-2,3-dione and 1,3-dimethylurea does proceed in aqueous sulphuric acid at room temperature and carbon-13 nmr evidence shows that the product is again (33d). We attempted to demonstrate formation of formaldehyde in this reaction mixture by blowing through nitrogen and passing this gas into a solution of dimedone, but the result was negative. However, it is known (Schow, 1929) that, in acid solution, formaldehyde forms a stable trimer and this may not be removed from the reaction mixture by the passage of nitrogen.

However, we were successful in isolating the 2,4-dinitrophenylhydrazone of formaldehyde from the reaction mixture. An excess of



R = Me

30



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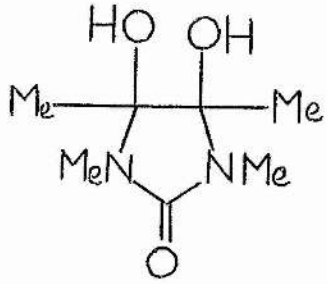

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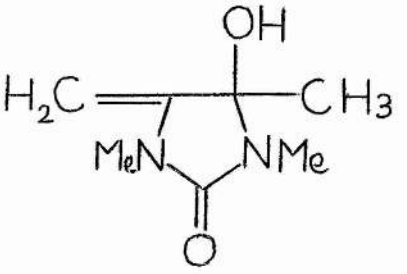
1,3-dimethylurea was used so that no unreacted butane-2,3-dione, which could itself form a DNP, remained. Addition of 2,4-dinitrophenylhydrazine to the reaction mixture after one hour yielded a yellow solid which was identified as the DNP of formaldehyde by a comparison of its proton nmr spectrum with that of an authentic sample. There is a characteristic double doublet centred at δ 6.96 ppm due to geminal coupling of the methylene group (36). We think, therefore, that the reaction mechanism involves elimination of formaldehyde. There are precedents for this in related reactions. The Friedel-Craft reaction of anisole with 2-t-butyloxirane to give 2-(4-methoxyphenyl)-2-methylbutane involves loss of a methylene group as formaldehyde (Inoue et al 1979).

Obviously formation of (33d) involves a number of intermediates. We attempted to detect some of these by examination of carbon-13 nmr spectra of the reaction mixture taken at intervals during five hours. However, it transpired that reaction is complete after half an hour, the time taken to collect the first spectrum. This spectrum did contain a few peaks in the range δ 84-103 ppm, in addition to those expected for (33d), and these can be assigned to polymers of formaldehyde. The same peaks were noticed in the spectrum of acidified formalin.

In considering the reactions of urea and 1-methylurea with diketones we have previously suggested that the first product of reaction is a diol (30), (37) in this reaction, and that further reaction is governed by the tendency of such compounds to eliminate the elements of water in the presence of acid. The intermediate (37)



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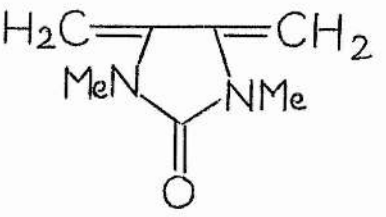


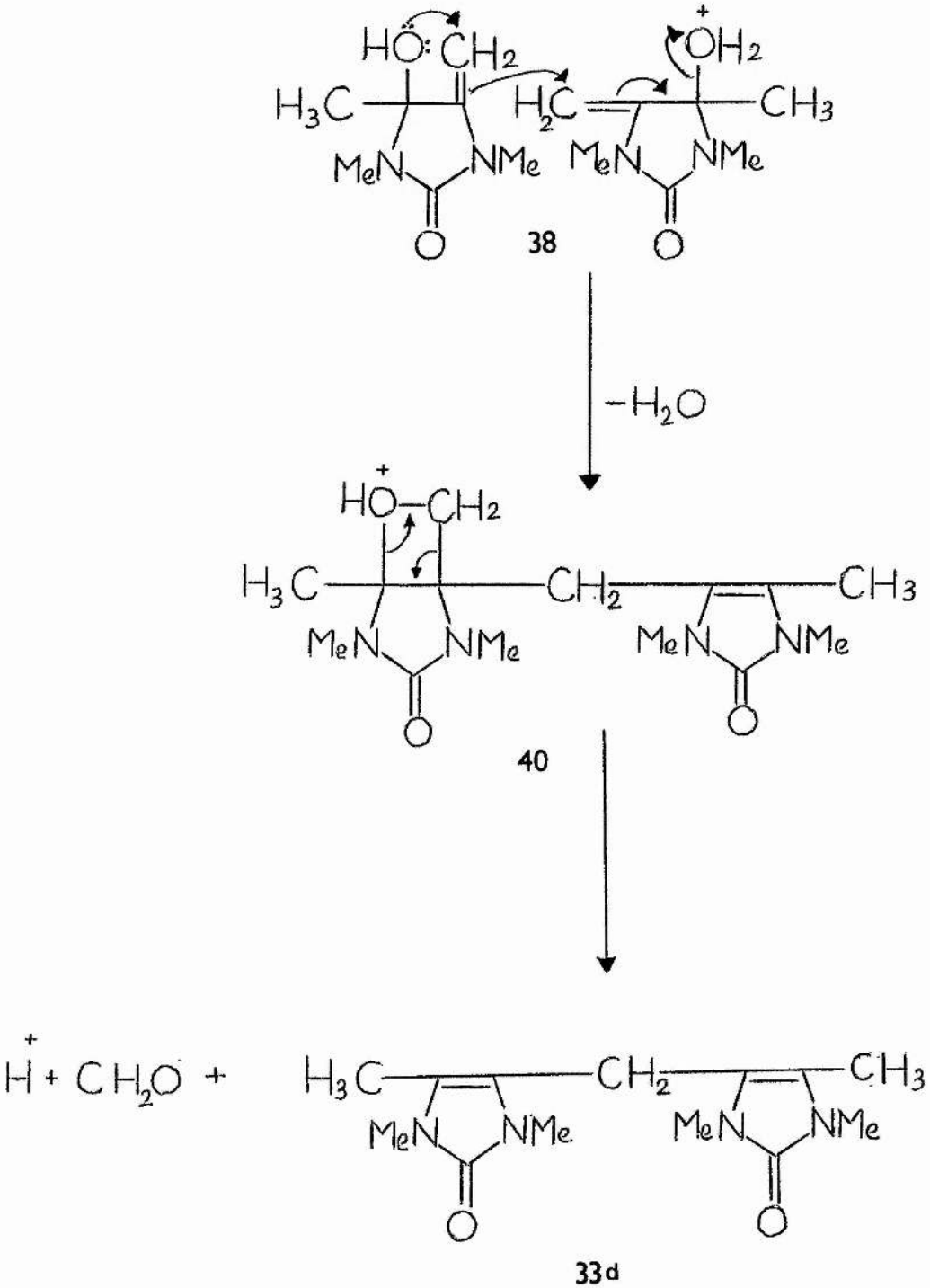
39

cannot form a double bond in the ring but can form one, or two, exocyclic double bonds, to give (38) or (39). The second of these cannot be the key intermediate as such a compound could not occur in the routes to (33a-h). On the other hand, compounds of type (33) form only if at least one substituent on the diketone is a methyl group and so (38) is a possible intermediate.

Compounds of type (33) are 4-imidazolin-2-ones which, as we will show later on, form readily under our experimental conditions, from acyloins and urea. However, there are two reasons why we reject the intermediacy of acyloins in a mechanism for the formation of (33) from a diketone. Firstly, conversion of a diketone to an acyloin requires reduction and our conditions are, if anything, oxidising. This is evidenced by the reaction of urea with benzoin, where products from reaction with benzil were obtained. Secondly, we were unsuccessful in effecting reaction between any acyloin and 1,3-dimethylurea. Compound (33d) forms readily from 1,3-dimethylurea.

Formation of (33d) does not appear to proceed by condensation of two molecules of butane-2,3-dione before reaction with 1,3-dimethylurea. The diketone was refluxed with benzene and TFA for 5 h, much longer than required for formation of (33d), but no water was formed. Apart from some tar, most of the diketone was recovered unchanged. Also, self-condensation is not catalysed by urea as no reaction occurred when 1,3-dimethylurea was replaced by 1,1,3,3-tetramethylurea.

These considerations lead us to suggest that (38) is the crucial intermediate in the formation of (33d) and that the departing carbon

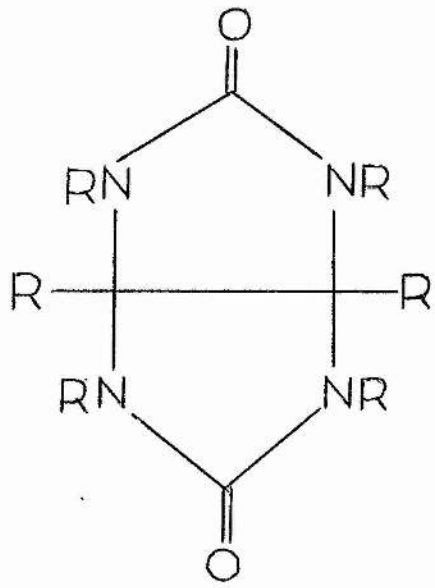

HO: CH2
H3C
MeN
NMe
O
38
+OH2
H2C
CH3
MeN
NMe
O
-H2O
+
HO-CH2
H3C
CH2
CH3
MeN
NMe
O
MeN
NMe
O
40
+
H + CH2O +
H3C
CH2
CH3
MeN
NMe
O
MeN
NMe
O
33d

SCHEME 7

leaves as formaldehyde. We propose the mechanism shown in Scheme 7. The condensation step is reaction of a molecule of (38) with another molecule which has been protonated to provide water as a leaving group. The driving force is the leaving of water and movement of the double bond, which generates an incipient carbonium ion on the exocyclic methylene group. Reaction of this with the electron-rich double bond of the other molecule of (38) and cyclisation to give an oxetane ring, although not readily predicted, is not unreasonable. The process envisaged is not unlike the acid-catalysed aldol condensation where one molecule of the enol form of acetone reacts with a molecule of the protonated ketonic form. Oxetane are known to decompose readily to give a double bond and a keto-compound. In a recent paper (Morelli, 1979) intermediate formation of an oxetane ring and decomposition to give a double bond in a steroid system has been proposed. Therefore, loss of formaldehyde from (40) to give (33d) is an expected process. Thus, we can rationalise the formation of (33d) with only the rather unexpected step involving formation of the oxetane ring. We have been unable to find any other reaction mechanism which accounts for the facts in as acceptable a manner.

All that was said in connection with reaction mechanism of 1,3-dimethylurea and butane-2,3-dione, equally applies to the reaction of 1-methylurea with 1-phenylpropane-1,2-dione.

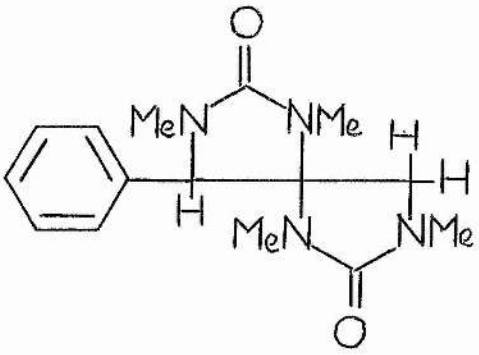
The product obtained from reaction of 1,3-dimethylurea with 1-phenylpropane-1,2-dione was a beautiful but intractable purple tar.



28

The intractable tar is well known, but the colour may make this one unique. However, neutralisation and extensive treatment by column chromatography led, eventually, to the isolation of crystals. The nature of purple colour will be discussed later. Molecular weight determination and elemental analysis gave a molecular formula for this product of $C_{15}H_{20}N_4O_2$. This corresponds to reaction of two moles of 1,3-dimethylurea and one mole of dione, with elimination of two moles of water. This immediately suggested a structure analogous to (28) with four NMe groups, but this was shown not to be the case.

The only distinctive and diagnostic feature of the ir spectrum was a strong absorption at 1710 cm^{-1} corresponding to an amide carbonyl. Methylation of the nitrogens appears to be responsible for increased solubility of the product and the proton and carbon-13 nmr were obtained by using [^2H]chloroform as solvent. The proton nmr spectrum at 100 MHz had four overlapping singlets at high field (δ 2.65-2.79 ppm), a singlet at δ 4.53 ppm, and a multiplet corresponding to the aromatic protons. The relative peak areas were 14:1:5, which gives the correct number of protons corresponding to the molecular formula, but indicates that the methyl group of the dione has not remained intact. Addition of a lanthanide shift reagent $(fod)_3Eu$ improved slightly the resolution of the high field peaks, giving relative peak areas of 3:3:8. This suggests that there is a methylene group with a chemical shift identical to that of two of the NMe groups. More successful resolution of this part of the spectrum came from spectra run at 220 and 360 MHz.

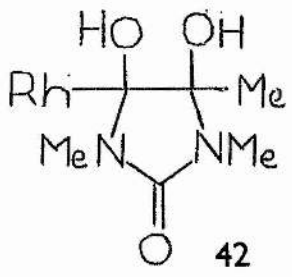


41

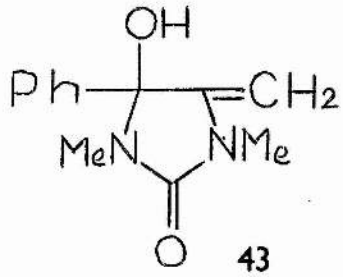
The four singlets are better resolved at 220 MHz and, more significantly, a doublet appears slightly downfield. The relative peak areas of the doublet and the overlapping singlets are 1:13. The doublet suggests geminal coupling of a methylene group with the other half of the double doublet buried in the overlapping singlets of the NMe groups. The 360 MHz spectrum gives a better picture. We suggest, therefore, that the structure of the product of reaction is 1,3-dimethyl-2-oxo-5-phenyltetrahydroimidazole-4-spiro-4'-(1',3'-dimethyltetrahydroimidazole-2'-one) (41). A model of the compound does indicate that there should be geminal coupling of the methylene group. The shift of the methine proton is at low field, but this is due to deshielding by the phenyl group.

This structure was confirmed by a study of the carbon-13 nmr spectrum. There are four peaks in the region δ 24.58-29.90 ppm corresponding to the NMe groups, four in the region δ 127.13-134.35 ppm corresponding to the phenyl ring, and one at δ 158.51 ppm due to the two carbonyl groups. There are three others, at δ 50.54, 66.49 and 77.89 ppm, and the shifts are consistent with structure (41). In the off-resonance spectrum these became a triplet, a doublet, and the low-field one remained as a singlet. This is exactly what is required for a methylene, a methine, and a tertiary carbon.

Compound (41) has a centre of chirality at the spiro carbon atom and must exist in two enantiomeric forms. However, an examination of a chloroform solution of (41) in a polarimeter showed that the product was racemic. The compound gave an intense blue fluorescence with a broad emission band originating at 350 nm.



42



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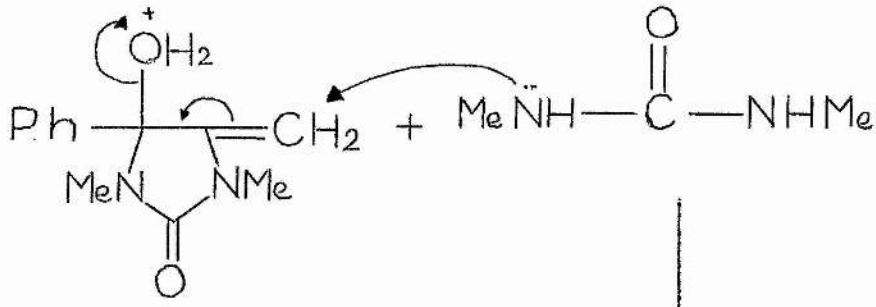

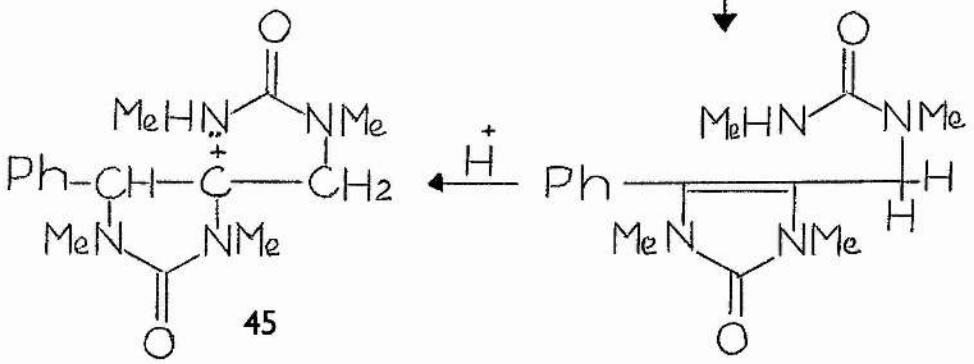

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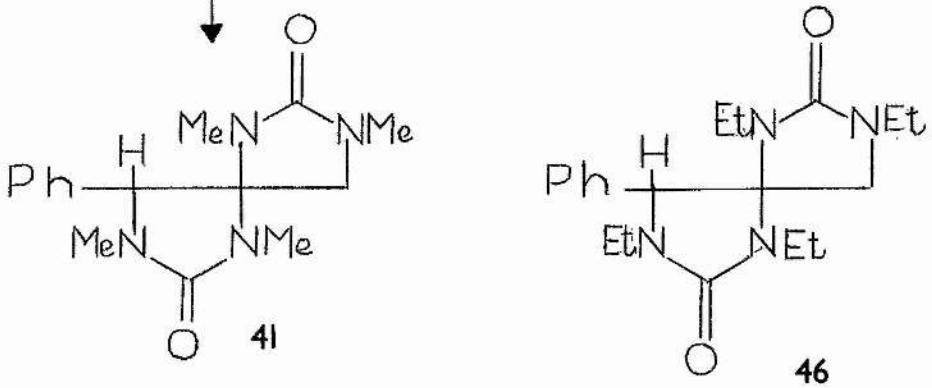


41

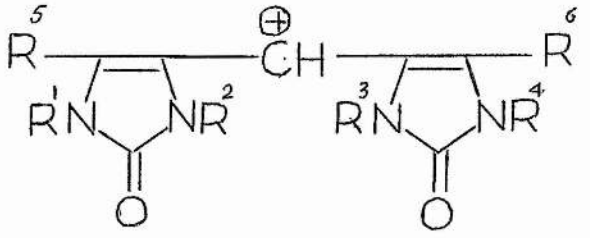
46

SCHEME 8

For the formation of (41) we see that the methyl group of the dione has become a centre of reaction. In our discussion of the reaction 1,3-dimethylurea and butane-2,3-dione we suggested an intermediate (37). Similarly, in this reaction, an analogous intermediate is (42), which, in the presence of methyl group permits elimination of water to give (43), analogous to (38). The protonated form of (43) can then add dimethylurea in the manner shown in Scheme 8.

Protonation of (43) at the hydroxyl group provides the molecule with a good leaving group (H_2O) and 1,3-dimethylurea can attack in a manner analogous to a Michael addition. This, on loss of a proton, gives the intermediate (44). Cyclisation of this compound can occur if the double bond is protonated. Admittedly the most favourable site for protonation is on the carbon removed from the phenyl group but this is a non-productive process. Protonation of the carbon adjacent to the phenyl group to give (45), even if a minor process, provides a cationic centre which can be attacked by the favourably disposed NHMe group and this, on loss of a proton, gives the desired product (41).

In light of the compounds previously discussed the structure (41) is sufficiently unexpected and we wanted to be certain that the N-methyl groups remained intact. So we examined the reaction of 1,3-diethylurea with the dione, which gave the expected product (46). The mass spectrum and elemental analysis of the product were in agreement with this structure, and the ir spectrum indicated amide carbonyl groups. The proton nmr spectrum had five sets of peaks. There were three sets of multiplet, with relative peak areas 12:8:5.



47

a $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = Me$

b $R^1 = R^4 = Me$, $R^2 = R^3 = H$, $R^5 = R^6 = Me$

c $R^1 = R^4 = H$, $R^2 = R^3 = Me$, $R^5 = R^6 = Me$

d $R^1 = R^3 = Me$, $R^2 = R^4 = H$, $R^5 = R^6 = Me$

e $R^1 = R^2 = R^3 = R^4 = H$ $R^5 = R^6 = Me$

f $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = R^6 = Ph$

g $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = Ph$

These clearly correspond to the methyl groups, the N-methylene groups, and the aromatic protons. There is a singlet at δ 4.56 ppm, due to the single methine proton, and a double doublet at δ 3.71 ppm (J 8 Hz). In this compound there is no overlapping of the N-ethyl groups and the methylene protons, and so the double doublet is observed in its entirety. The essential features of the carbon-13 nmr spectrum are the same as those of (41). The off-resonance spectrum produces a doublet, a singlet, and a triplet for the skeletal carbon atoms. This work has confirmed that the N-alkyl groups do, indeed, remain intact and provides additional proof of the structure of (41).

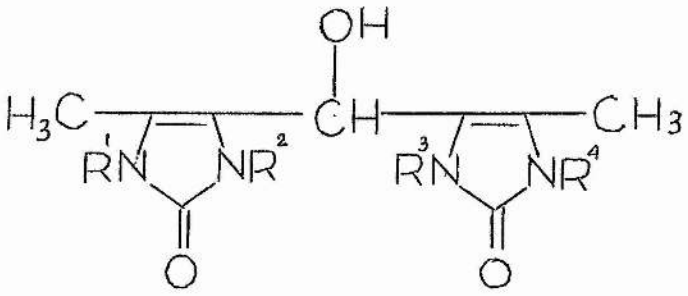
We now consider the colour reactions, and to find a species which is responsible for the colour development. The reaction mixture from which (33d) was obtained was deep purple and we found that we could generate this coloured material from (33d). Acidification of an aqueous solution gave a purple solution, the intensity of which increased with time. The rate of colour intensification was increased by blowing oxygen through the solution and by addition of an oxidising agent. Compound (33d) is a 'skipped' diene and therefore readily susceptible to radical oxidation at the methylene group to give a hydroperoxide (Chan et al, 1978). Protonation of this and elimination of hydrogen peroxide would give the carbonium ion (47a), which is related to the cyanine dyes. The positive charge can be delocalised on one of the two outer nitrogens with formation of a conjugated, chromophoric system. This, we suggest, is the origin of the colour. The reaction is analogous to the generation of the tropylium ion from cycloheptatriene by

autoxidation in strong acid (Borg et al, 1962).

A solution of (33d) in chloroform is initially colourless but turns purple on standing. Chloroform normally contains some acid due to oxidation. Formation of colour is diminished if light and oxygen are excluded. However, addition of phosphorus pentachloride (a Lewis acid) resulted in immediate production of the colour. Lewis acids generate carbonium ions and are known to convert cycloheptatriene into the tropylium cation (Vol'pin, 1957).

Formally (47a) is generated from (33d) by removal of a hydride ion and further proof of the identity of the coloured species came from the reaction of (33d) with triphenylmethyl perchlorate (Dauben et al, 1960). The colour appeared immediately. Thus, formation of (47a) is proved beyond doubt and we now know what highly coloured species may be formed by reaction of ureas with α-diketones.

The filtrate obtained after the removal of the mixture of (28c) and (28d) and of (28a) from the reaction mixture was highly coloured and suggested formation of another reaction product. In view of our identification of the coloured material obtained by reaction of 1,3-dimethylurea as the carbonium ion (47a) it seems probable that the above colours are due to (47b) and (47c). As has been seen in the discussion of the mechanism of (33d), there is nothing to stop urea and 1-methylurea reacting in the same. However, we were unsuccessful in isolating and characterising (33e-e') or (33f) from the coloured filtrates. It is possible that carbonium ion formation is complete and neither (33e-e') or (33f) is present. With the reaction of 1,3-dimethylurea some (33d) must remain unreacted,



48

a $R^1 = R^4 = Me,\ R^2 = R^3 = H$

b $R^1 = R^4 = H,\ R^2 = R^3 = Me$

c $R^1 = R^3 = Me,\ R^2 = R^4 = H$

d $R^1 = R^2 = R^3 = R^4 = H$

although the colour of the solution does indicate that (47a) forms spontaneously. With 1-methylurea and urea the main products of reaction are, of course, (28c-d) and (28a); these are highly insoluble and immediately removed from the reaction mixture, leaving little material to form (33e-e') and (33f).

Some evidence was obtained for formation of (47b). Removal of solvent from the filtrate left a yellow gum which did not crystallise, but a cream solid was obtained on neutralisation of a methanolic solution by aqueous ammonia and addition of acetone. As this material was filtered off it became dark brown on contact with air. However, this was avoided when filtration was carried out under dry nitrogen. Once the material was obtained dry it was stable in a tightly sealed container. Addition of a little of this material to water produced a deep golden solution. It was found to be insoluble in all the regular organic solvents and, therefore, we were unable to purify it be recrystallisation.

The material was hygroscopic, as well as impure, and no meaningful elemental analysis could be obtained. The proton nmr spectrum (in D_2O) corresponds to methyl and N-methyl groups and there was a very large H_2O peak. The ir spectrum (KBr disc) had a broad peak in the NH/OH region and another in the region C=C/C=O. Alkaline potassium permanganate was decolorised by a solution of the material, suggesting the presence of carbon-carbon double bonds. We suggest that the material isolated is the carbinol (48), probably as a hydrate, which, in solution, forms the coloured carbonium ion (47b-c).

There is support for this from the carbon-13 nmr spectrum in aqueous solution. There are peaks centred at δ 26.07, 55.26, 60.41 and 161.51 ppm corresponding to methyl, two N-methyl groups, and the carbons of the double bond which, because of the positive charge, have all moved downfield from the equivalent values in (33d). The carbonium ion centre and the carbonyl group did not appear in the spectrum.

We were equally unsuccessful in obtaining positive direct identification of the coloured product by reaction of urea and butane-2,3-dione. Repetition of the isolation procedure described above yielded a cream solid which was hygroscopic, air-sensitive, and soluble only in water. However, we are sure that the colour is due to (47e), partly because of the evidence adduced for the formation of (47a), and partly because we have found it impossible to find any other suitable chromophoric system which can form from urea and α-diketone. This identification is important as reaction between urea and diacetyl monoxime in acid is used as a colorimetric procedure for the measurement of urea concentrations in biological liquids during medial diagnosis (Wybenga et al, 1971). The method is widely used and appears to be highly specific for urea. Until now the chemistry has been unknown. In acid solution the monoxime is hydrolysed to the diketone which then, we suggest, reacts with urea to form (33f). Radical oxidation of (33f) in acid solution generates the coloured species (47e). In the very dilute solutions used in biological assays (28a) is not precipitated. When

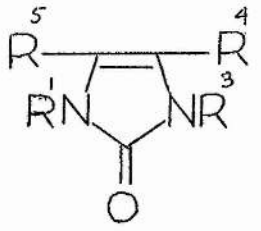
(28a) is dissolved in concentrated acid it is converted into (47e) and exhibit an identical absorption maximum (478 nm) as the cream solid isolated from filtrate after the removal of (28a). It has been suggested (Wootton, 1974), that the colour is photo-sensitive, intensified by the presence of ferric ions and semi-carbazide. After a series of experiments as mentioned in the experimental section, we have found that colour formation depends only upon the strength of acids and boiling-time, and not on any kind of ions (eg. Fe^{3+}, Fe^{2+}, PO_4^{3-}, Cl^-, $NH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2\text{-}NH_2$). But, on the other hand, the presence of hydroquinone diminishes the colour intensity and reflects the role of dissolved oxygen in solution. Similar observations were noted in the reaction of other ureas and diketones.

In the reaction of 1,3-dimethylurea and 1-phenylpropane-1,2-dione, the main product is (41) leaving behind a small amount of coloured material. It was not enough to proceed further. However, in the light of the proposed reaction mechanism there is no reason why two molecules of (43) do not condense in the same way as that shown in Scheme 7. Thus, we assume, the coloured material is (33g) which, in acid solution has converted to (47f). The carbon skeleton of (41) in strong acid does not remain intact, but slowly changes to (47f) along with a series of colour variations (λ_{max} is the same).

The highly coloured filtrate left after the isolation of (28g) was enough to undertake further investigations. Addition of excess acetone brought out a white solid, which melted at 310°. On

exposure to air and light it slowly changed to pink colour. Elemental analysis and molecular weight determination correspond to a molecular formula $C_{19}H_{16}N_4O_2$. The proton nmr spectrum in [$^2H_6$]DMSO shows all the characteristic features present in (33h). Apart from NH protons, the methylene protons absorb at δ 3.75 (2H) while aromatic ones at 7.25 (10H) ppm. The carbon-13 nmr spectrum unambiguously confirms the structure of $C_{19}H_{16}N_4O_2$ as (33h). Besides resonances of aromatic carbons, there are four peaks at δ 20.72, 114.69, 118.13 and 154.02 ppm. The first and last peaks are assigned to methylene and carbonyl groups, while the remaining two are due to unsymmetrical olefinic carbons. The decolorisation of neutral solution of potassium permanganate further establishes the existence of olefinic double bonds in (33h). The ir spectrum is equally consistent with NH and amide carbonyl groups. On acidification it yields an intense purple colour and this colour absorbs at the same wavelength (550 nm) in the visible region as the filtrate from which it has been recovered. Hence, the structure of (33h) which is analogous to (33d) , is confirmed.

Compounds of type (33) contain 4-imidazoline-2-ones on either side of the methylene group. We thought it would be of interest to examine the reaction of ureas and acyloins, as the resulting product, 4-imidazolin-2-ones, might condense to give products analogous to (33). That is why we investigated the reactions of urea, 1-methylurea, and 1,3-dimethylurea with various acyloins under standard conditions, ie. in refluxing benzene with added TFA. Detailed spectral data of the products are given in the Experimental section.



50

a $R^1 = R^3 = H, \quad R^4 = R^5 = Me$

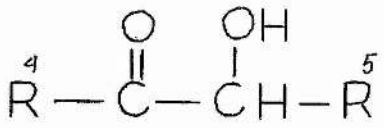
b $R^1 = R^4 = R^5 = Me, \quad R^3 = H$

c $R^1 = R^3 = H, \quad R^4 = R^5 = Et$

d $R^1 = R^3 = H, \quad R^4 = Me \quad R^5 = Ph$

e $R^1 = R^4 = Me, \quad R^3 = H, \quad R^5 = Ph$

f $R^1 = Me, \quad R^3 = H, \quad R^5 = R^6 = Ph$



49

a $R^4 = R^5 = Me$

b $R^4 = R^5 = Et$

c $R^4 = Me \quad R^5 = Ph$

d $R^4 = R^5 = Ph$

a) Acetoin (49a) - Reaction with urea proceeds readily to give the expected product 4,5-dimethyl-4-imidazolin-2-one (50a) (Blitz, 1907). With 1-methylurea we obtained 1,4,5-trimethyl-4-imidazolin-2-one (50b), which was identified mainly from the carbon-13 nmr spectrum: two nearly identical methyl groups, one N-methyl group, two olefinic carbons with slightly different shifts, and one carbonyl carbon. The formation of (50b) does not agree with the statement "the acyloins of the aliphatic series (which) fail to react with substituted ureas"(Hofmann, 1953). However there was no reaction between acetoin and 1,3-dimethylurea.

b) Propionoin (49b)

Reaction with urea gave the expected product, viz (50c), which was identified by spectral data. With 1-methyl- and 1,3-dimethylurea unreacted starting material was recovered. Lack of reaction with the former, when compared to reaction with acetoin, must be due to increased steric factors.

c) Phenylacetylcarbinol (49c)

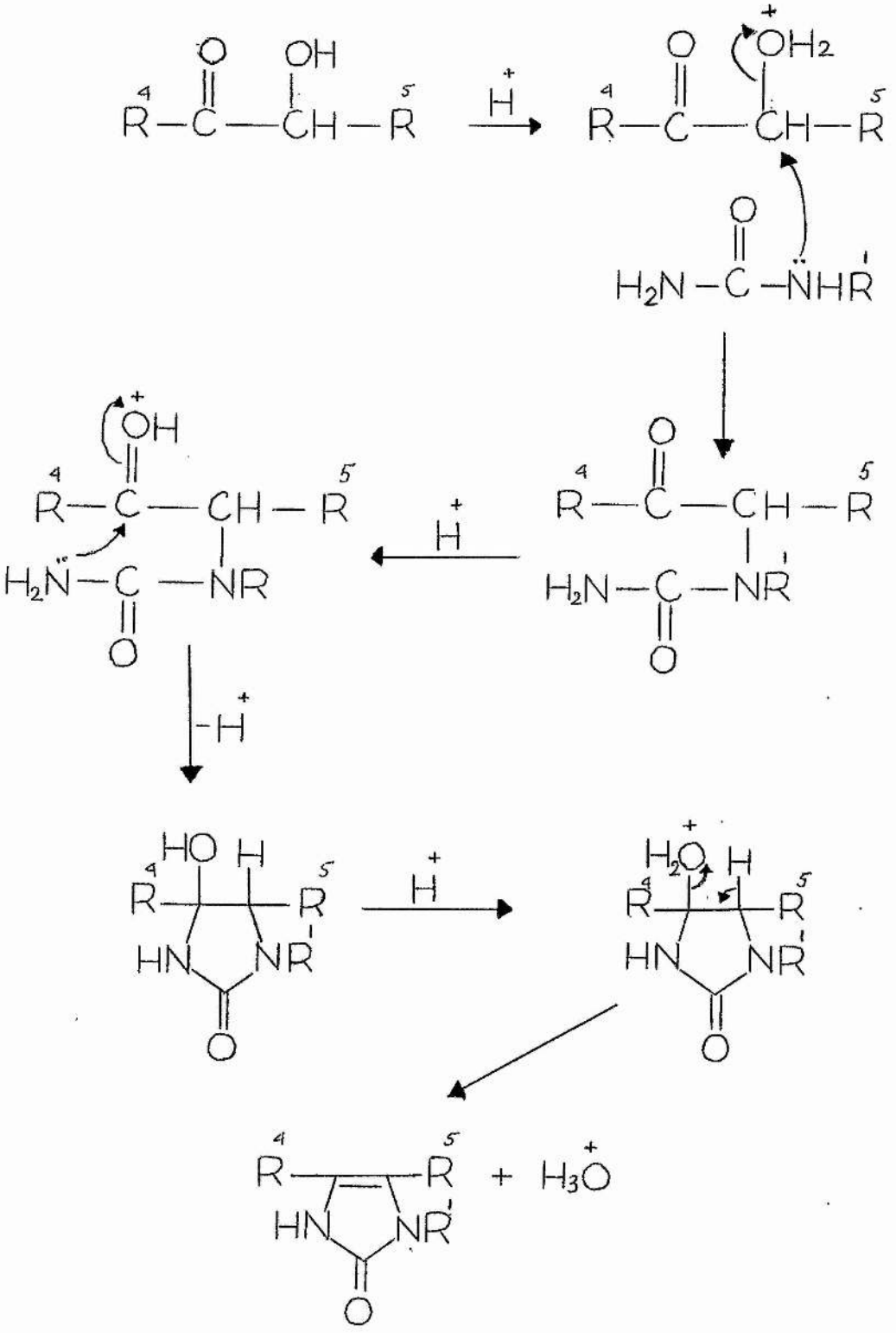
Reaction with urea gave the expected product (50d). All the spectral data are consistent with this structure. There was also reaction with 1-methylurea but, as the acyloin is unsymmetrical, there is the problem of the position of the N-methyl group. In the proton nmr spectrum of (50b) the protons of the N-methyl group have a chemical shift of δ 3.12 ppm, while those of the present compound are at δ 2.48 ppm. This upfield shift suggests that the methyl group is adjacent to the phenyl group with

consequent magnetic shielding. The product is, therefore, (50e). All the other spectral data are in agreement with assignment. 1,3-Dimethylurea did not react with phenylacetylcarbinol.

d) Benzoin (49d)

Reaction with urea gave a product which was identified with that obtained by reaction of urea and benzil (28g). This has been prepared and characterised previously (Butler and Leitch, 1980). Benzoin is known to oxidise readily to benzil and this is the simplest explanation of the above observation. With 1-methylurea the situation is more complicated. The product, which is insoluble in every solvent suitable for recrystallisation, did not melt sharply. This suggested that it was a mixture. Benzil is known to react with 1-methylurea to give (28h) but the proton nmr spectrum of this product had chemical shift of δ 2.96 and 3.14 ppm corresponding to two different N-methyl groups, only one of which is right for (28h). We assume that this is due to concomitant formation of (50f) and (28h). The mass spectrum of the product had peaks at m/e 280 and 322, which are molecular ion peaks for the two products. Other spectral data were not diagnostic. It appears that reaction of benzoin with methylurea occurs at a rate similar to that of oxidation to benzil.

Under our experimental conditions there was no reaction between benzoin and 1,3-dimethylurea, although it is claimed (Hofmann, 1953) that reaction can occur to give 1,3-dimethyl-4,5-diphenyl-4-imidazolin-2-one. Our results do not support the view that, in reaction with N-substituted ureas, acyloins of the



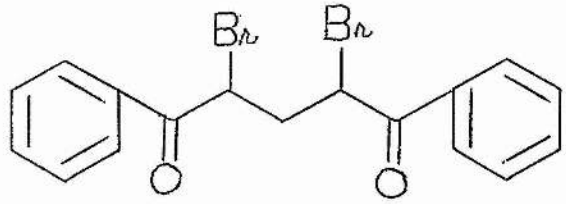
SCHEME 9

aliphatic series react differently from those of the aromatic. The simplest explanation for the lack of reactivity of 1,3-dimethylurea is a steric one.

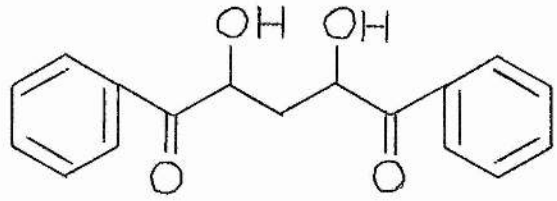
We propose a general mechanism, shown in Scheme 9, for the reaction of urea with acyloins in the presence of an acid. Like other reactions of ureas and diketones, here also, the driving force is the elimination of the elements of water whenever this is possible. The need for the carbon atom to which R^5 is attached to lose two groups, H and OH, means that reaction probably occurs here first. The formation of (50e) from (49c), rather than the other isomer, is in agreement with this as the methylated nitrogen is the more basic site and will attack first.

All the imidazolin-2-ones prepared, apart from (50f) gave intense colours in acid solution. We were successful in isolating beautiful crystals of crimson colour from chloroform solution of (50b) when it was saturated with dry hydrogen chloride gas. Its mass spectrum does indicate the presence of chlorine and the highest peak was at m/e 300. It melts at 100° (not sharp) and elemental analysis (only C, H, N) agrees with the simplest formula of $(C_3H_5N)_n$. Other spectral data correspond to original features of (50b). It is extremely soluble in water and yields red solution. However, we cannot speculate on the reaction pathway when the final structure of product is still unknown.

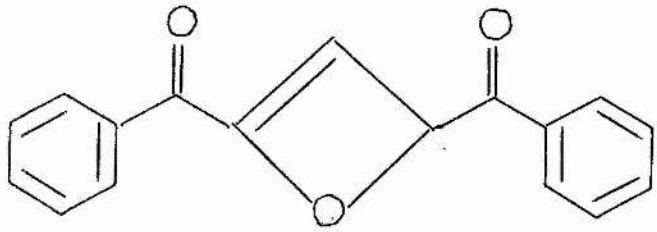
After a detailed study of the reactions of ureas with diketones and acyloins, we decided to synthesise such a compound which could replace diacetyl in the estimation of urea concentrations in biological liquids. After a prolonged and tedious struggle we



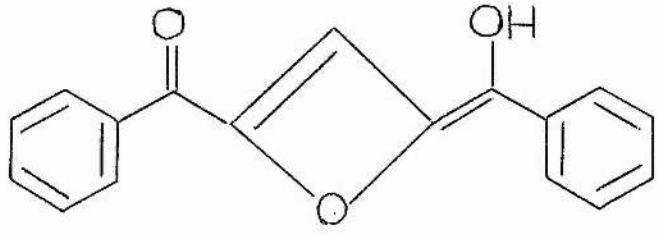
51



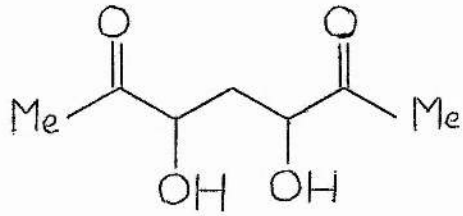
52



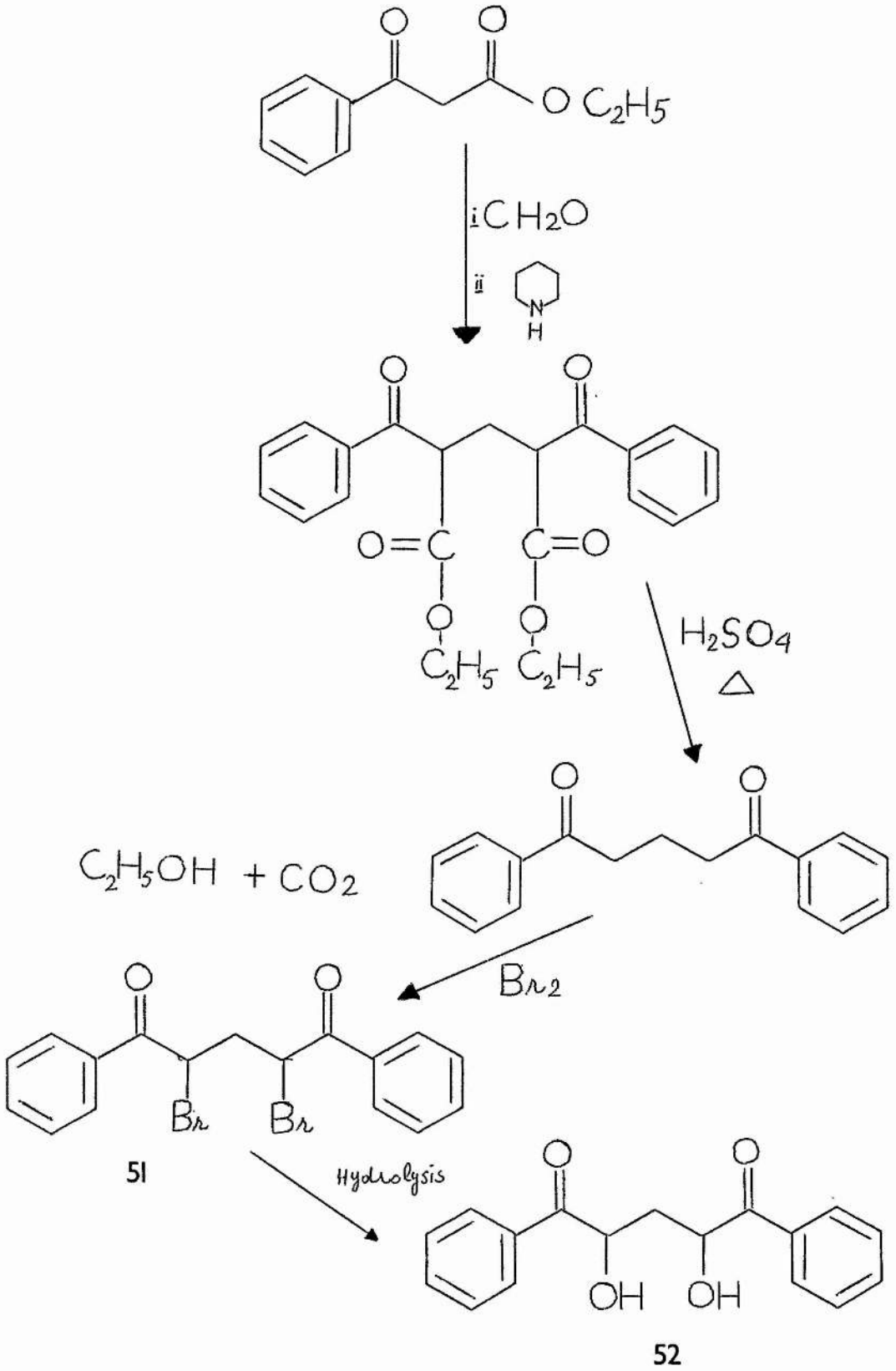
53



53a



54


O C2H5
i CH2O
ii
N
H
O=C
C=O
C2H5 C2H5
H2SO4
△
C2H5OH + CO2
Br2
Br
Br
51
Hydrolysis
OH OH
52

SCHEME 10

succeeded in synthesising 1,5-diphenyl-2,4-dihydroxypentane-1,5-dione (52) (30% yield) along with (53) which is a major product (Scheme 10). Unfortunately, this compound (52) did not react as we expected, at room temperature. However, refluxing (52) with urea in benzene and TFA gave a red viscous mass which on dilution with water yielded red coloration, a small amount of (53), and some unidentified material. The red colour of aqueous solution does indicate that compound (52) has probably reacted with urea and subsequently formed a carbinol, which is a precursor of coloured species. As compound (52) posed solubility problems in addition to a dramatic stabilising-effect of benzoyl group on either side in the formation of (53), we suggest another compound (54), analogous to (52), which could be a substitution for diacetyl.

Compound (52) is a white crystalline solid, melts at 144° while compound (53) is a greenish yellow solid, exists predominantly in enolic form (53a) in solution and, has mp 244°. Other relevant data are given in Experimental section. As compound (52) has two centres of chirality and must exist in two enantiomeric forms. However, the proton nmr spectrum at 100 MHz showed that the product was diastereoisomers and, probably contained meso form.

The last α-diketone left is cyclohexane-1,2-dione. This dione also gave an intense blue coloration with urea and its N-alkyl derivatives. The most readily characterised product was obtained on treatment with 1,3-dimethylurea. Reaction was effected in the manner described previously and a white solid was recovered

a $R = Me$

b $R = H$

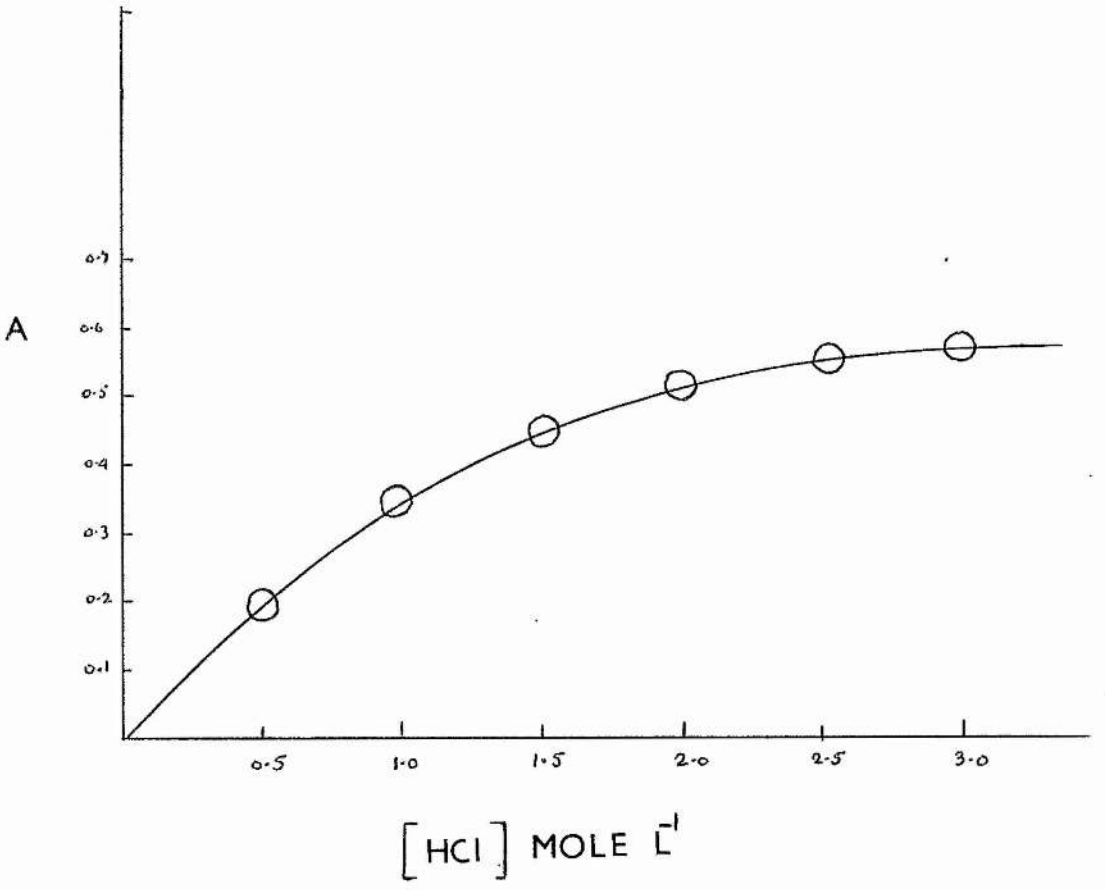
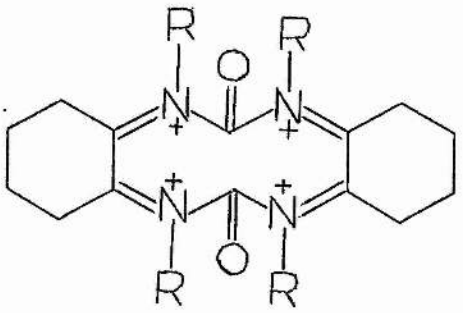


FIG. 1

from the reaction mixture. On heating, this material lost water before melting. In the mass spectrum there was a peak at m/e 328 but clearly this may be the molecular ion after loss of one or more molecules of water. The material was soluble in both chloroform and water. Elemental analysis gave an empirical formula of $C_9H_{16}N_2O_3$. The ir spectrum indicated the presence of carbonyl and hydroxyl groups. From the evidence so far we propose structure (55a) and the peak at m/e 328 in the mass spectrum is ($\underline{M}^{+}$-$4H_2O$). The nmr spectra of the product gave confirmation of this structure. In the proton nmr spectrum at 100 MHz there were two singlets at δ 1.82 and 2.30 and a collection of unresolved singlets in the range 2.76-3.77 ppm. The pair of singlets we assign to the ring methylene groups and the others to N-methyl groups. Compound (55a) may exist in a number of stereoisomeric forms and so the N-methyl groups are in different magnetic environments. The spectrum at 360 MHz was not more informative; it improved on the one at lower field only in that the N-methyl peaks were better resolved. The carbon-13 nmr spectrum was more diagnostic and indicated, as well as N-methyl and carbonyl groups, three carbon atoms of different shifts in the molecule. These are the carbon atoms of the cyclohexane ring and one, with a shift of δ 58.0 ppm is right for a carbon atom bearing a hydroxy group.

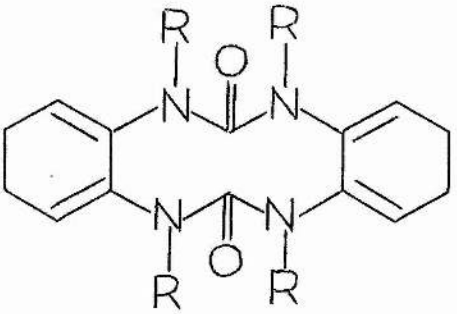
Addition of (55a) to moderately concentrated HCl produced a purple solution which changed to yellow on standing. This reaction could be due to protonation of the hydroxy groups followed by loss



56

a $R = Me$

b $R = H$



57

a $R = Me$

b $R = H$

of water to give a conjugated cation. If all hydroxy groups were protonated then the product would be (56a), a conjugated tetracation. The conjugation explains the colour. The carbon-13 nmr spectrum of (55a) dissolved in 5M hydrochloric acid had no peak at δ 58.0 ppm indicating loss of all the hydroxyl groups. There is also a peak at δ 151.2 ppm which we can ascribe to the C=N group of (56a). The formation of tetracation is surprising but it is not without precedent. All four nitrogens of hexamethylene tetraamine are protonated in sulphuric acid solution (Gillespie and Wasif, 1953). The coloured species is not stable and it could react further by slow deprotonation and formation of olefinic double bonds to give a molecule (57a) which is no longer conjugated. An aged solution of (55a) in 5M hydrochloric acid does have peaks in the range δ 120.3-128.4 ppm in the carbon-13 nmr spectrum.

The purple solution is just stable enough to permit determination of the concentration of the coloured species as a function of acidity. The absorbance went on increasing with acid strength and finally levelled at concentration of 3M HCl (Figure 1). But the isosbestic points and λ_{max} remained fixed as the acidity was increased. This is not what is expected if stepwise protonation occurs, ie. complete conversion to the monocation before a second protonation commences. The spectral evidence accords better with partial conversion to the final product viz. the tetracation (56a). The extensive conjugation in (56a) may be the driving force in this reaction. The only species present in acid solution are therefore, (55a) and (56a), excluding any products of proton loss from (56a). Therefore, we were able to measure spectrophotometrically the ratio $[(56a)]/[(55a)]$ as a

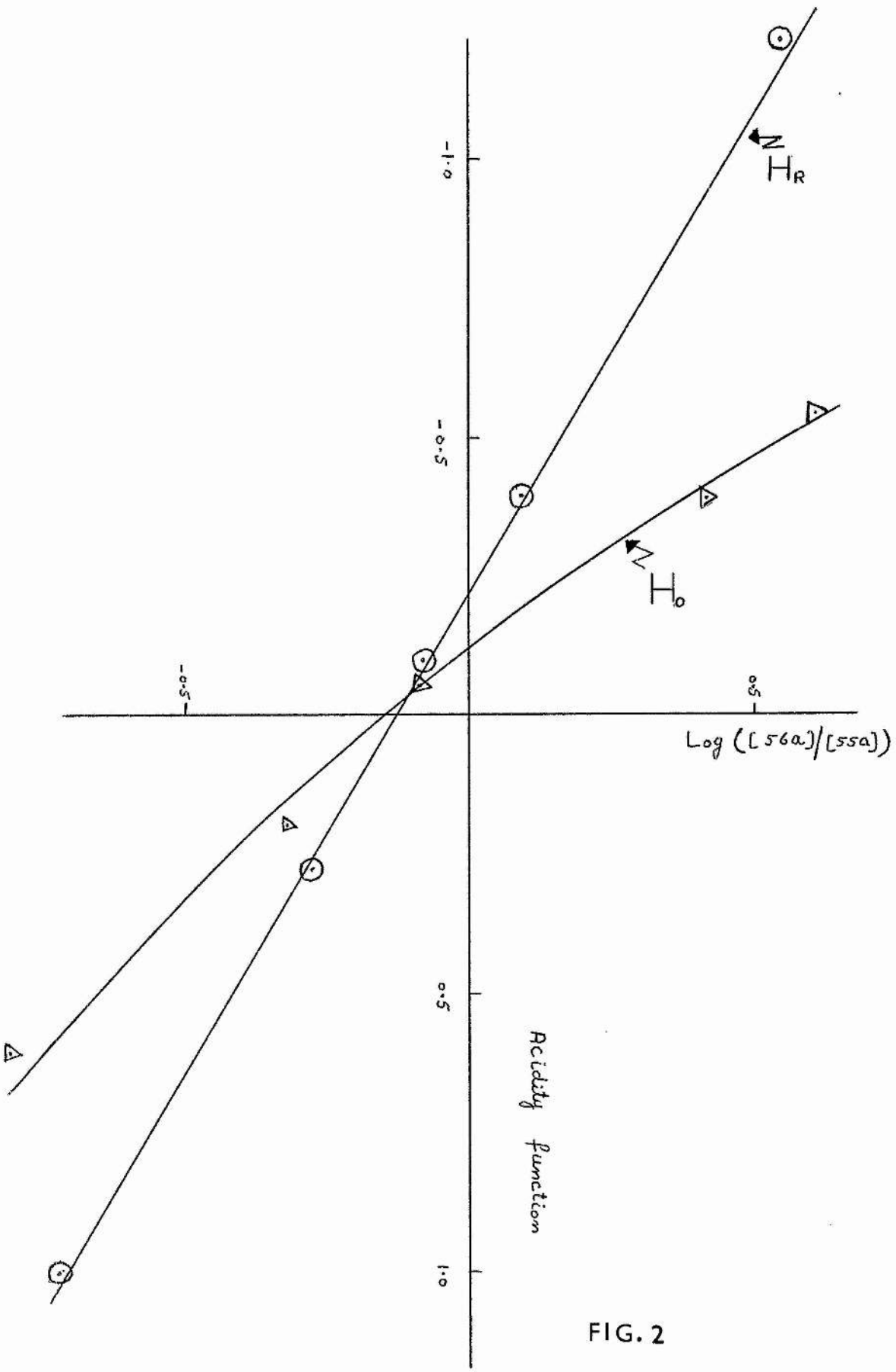


FIG. 2

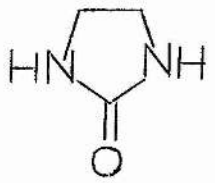
Variation in the absorbance of (55a) at 580 nm with acidity

function of acid concentration. The term log [(56a)]/[(55a)] was plotted against two acidity functions $\underline{H}_o$ and $\underline{H}_R$ (Figure 2). With the latter the curve is rectilinear and has a slope of -0.7. A correlation with $\underline{H}_R$, rather than $\underline{H}_o$, is right for a process involving protonation of an hydroxyl group and loss of water and supports the proposed chemical changes. However, we are unable to give meaning to the magnitude of the slope.

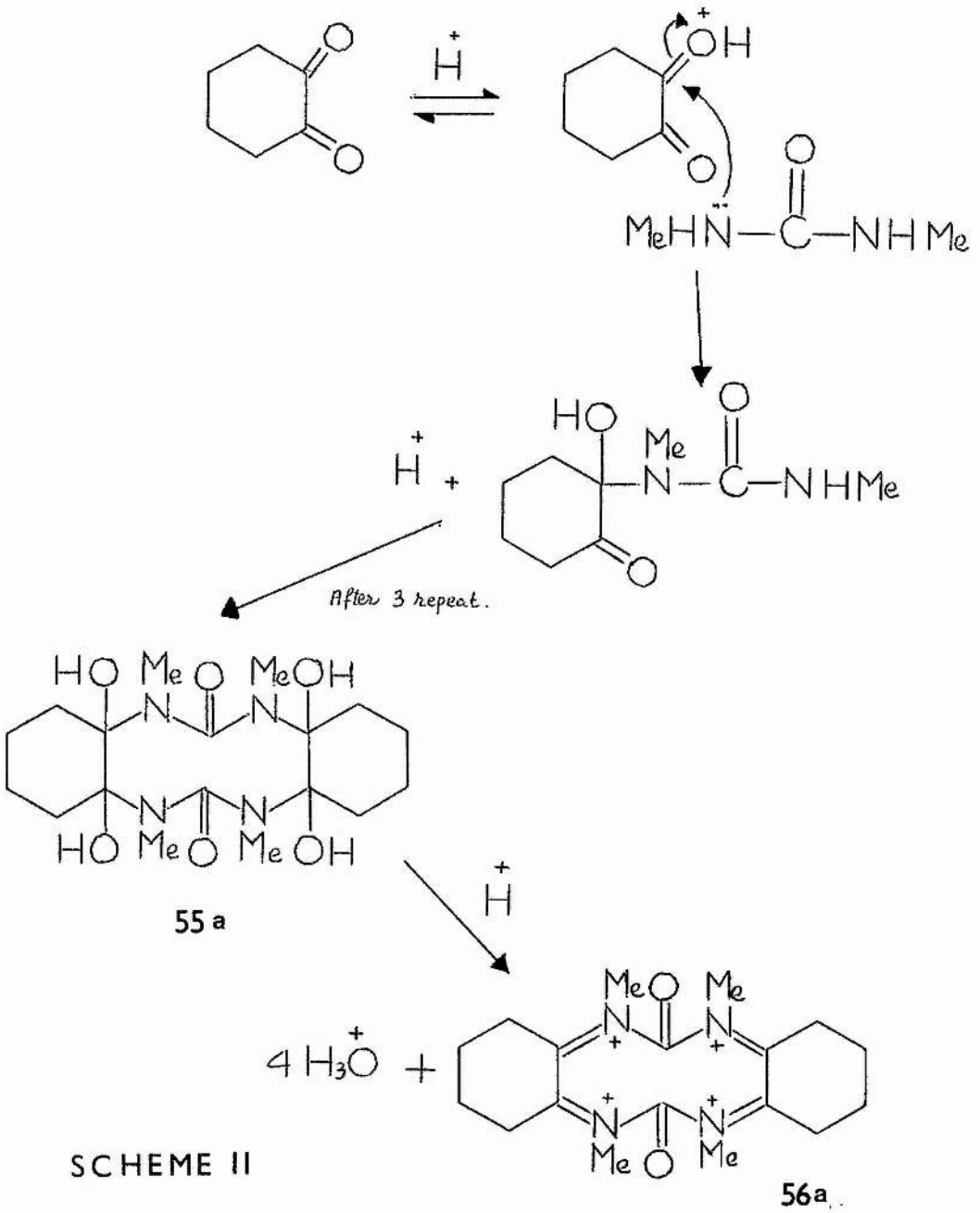
Reaction of urea and cyclohexane-1,2-dione under the same conditions gave a white solid which also produced an intense colour when dissolved in acid. This product was more difficult to characterise, partly because of its low solubility. The ir spectrum suggested the presence of NH/OH groups and carbonyl groups and, from elemental analysis, the empirical formula is $C_{17}H_{12}N_2O_3$. Extensive fragmentation occurred in the mass spectrometer and so it was not possible to determine the molecular weight by this method. However, the evidence so far is consistent with a structure which is an analogue of (55a) without N-methyl groups, ie. (55b). Unlike (55a), this compound is not soluble in the solvents regularly used for nmr spectroscopy, but does dissolve in trifluoroacetic acid (TFA). Intense colours develop rapidly if the solution is warmed, but at ambient temperature the reaction is slow enough to allow recording of the proton and carbon-13 nmr spectra. Provided the TFA solution was not allowed to stand for too long, it was possible to recover the material from solution unchanged. In the proton nmr spectrum there are two broad singlets at high field, which we assign to the hydrogens of the

cyclohexane ring, and a broad singlet at much lower field (NH and/or OH). The carbon-13 nmr spectrum is more informative; resonance occurs at δ 17.6, 31.8, 79.4, and 165.5 ppm. The first two we assign to the cyclohexane methylene groups, the third to the carbon bearing a hydroxy group, and the last to the carbonyl groups.

As mentioned previously, a solution of (55b) becomes intensely coloured on warming. This is of relevance to analytical biochemistry. Reaction between urea and the dioxime of cyclohexane-1,2-dione (nioxime) has been proposed (Siest, 1967) as a colorimetric method for the determination of urea concentrations in biological fluids. From the work described above we conclude that the analytical reaction involves hydrolysis of the dioxime to cyclohexane-1,2-dione and reaction with urea to form(55b). Protonation and loss of water gives the coloured tetracation (56b) and this is the chromophore. The colour developed depends upon the acidity, the temperature, and the time of heating. In the words of the original report (Siest, 1967) "The colour is intense at the start, when violet. Then changes slowly, going blue to green". The lack of colour stability has probably been responsible for the infrequent use made of the procedure. Otherwise it does have a number of advantages over the use of diacetyl monoxime. We suggest that the changing colours described by Siest (1967) are due to deprotonation of (56b) to give molecules containing one, two, three and four double bonds. The final product is (57b). Elucidation of the chemistry involved in these colour changes does not immediately suggest a way of improving the reaction



58


H+
MeHN—C—NHMe
HO
Me
N—C—NHMe
H+ +
After 3 repeat.
HO Me O Me OH
HO Me O Me OH
55 a
H+
4 H3O+ +
Me Me
Me
56a

SCHEME II

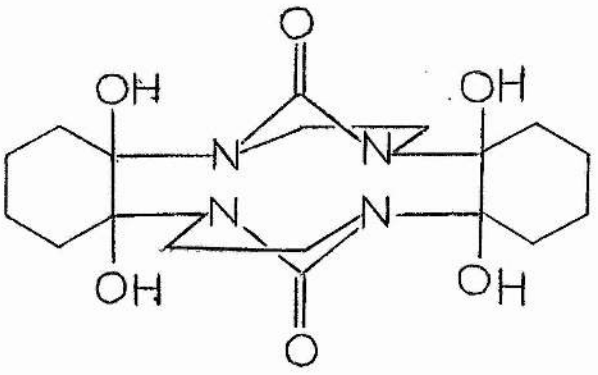
as an analytical procedure.

Reaction of 1-methylurea with cyclohexane-1,2-dione also gives an intense blue coloration similar to that as described in the case of urea and 1,3-dimethylurea. But, the past experience on reactions of α-diketones with 1-methylurea reflects that reaction can take place leading to products, which are analogous to (55), with a number of isomers pertaining to the positions of N-methyl group. However, we do not think that it will remain worthwhile to proceed further with 1-methylurea.

We can now compare the reactions of cyclohexane-1,2-dione with a non-cyclic analogue, diacetyl. The latter reacts with urea to give, initially, the bicyclic compound (28). Models indicate that the equivalent compound from cyclohexane-1,2-dione is so crowded as to resist formation. The reaction, therefore, takes a different course and the much less crowded compound (56) is formed. The mechanism for the formation of (56a-b) is quite straight forward: protonation of the keto- group and attack of the cationic centre thus created by the nucleophile urea (Scheme 11).

Diacetyl and 1,3-dimethylurea react to give the unexpected product (33d) and reaction involves loss of a methyl group. A parallel reaction with a cyclic diketone is not possible and so the product is analogous to that obtained on reaction with urea.

Now, we turn to the reactions of 2-imidazolidinone (58) with α-diketones. This compound (58) is so closely related to 1,3-dimethylurea that we hoped it might react in a similar manner to give a number of unusual polycyclic compounds. In this we were disappointed. However, the product obtained from diacetyl

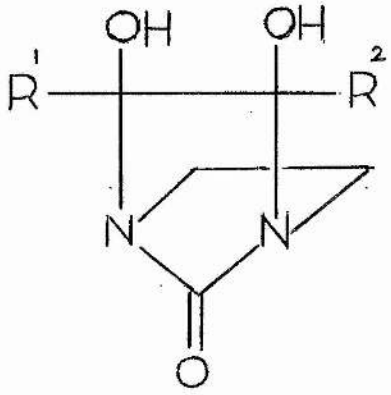


59

and (58) appears to be polymeric. The mass spectrum was typical for that of a polymer with the peak of highest m/e value at 264. At low ionisation the peak at m/e 348 was observed. In the ir spectrum there was no sign of any hydroxyl groups. The proton nmr spectrum indicated the persistence of methyl and N-methylene groups in the product but the ratio of integrations is 1:2, rather than 3:2 as would be expected for material formed from equal numbers of molecules of diacetyl and (58). We are unable to deduce a structure for this polymer.

There was some evidence of reaction between 1-phenylpropane-1,2-dione and 2-imidazolidinone (58) took place but an intractable tar was obtained.

The final experiment in this series was the reaction of a cyclic α-diketone, ie. cyclohexane-1,2-dione and (58). No tar formed and a light brownish crystalline product was obtained. On heating the product water was evolved before the material melted. The peak at highest m/e in the mass spectrum was at 274, which is not easy to accommodate. The ir spectrum indicated the presence of hydroxy and carbonyl groups. The proton nmr spectrum suggested the presence of hydroxy protons, N-methylene protons, and cyclohexane protons in the ratio 1:2:4 and, on the basis of this spectrum, we propose structure (59). The number of possible stereoisomers of (59) makes the carbon-13 nmr spectrum complex. However, in the spectrum there is evidence for four different types of carbon atoms in the molecule: ring methylene groups, carbons bearing an hydroxyl group, and carbonyl groups. Although



60

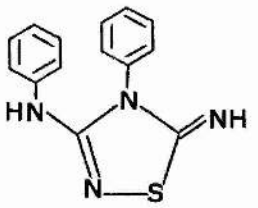
a $R^1 = R^2 = Ph$

b $R^1 = Me$ $R^2 = Ph$

the spectrum is too complex to confirm the proposed structure, yet there is nothing in it which is inconsistent.

Compound (59) does not give intense colours in acid solution. The nitrogen-to-nitrogen bridge enforces a stereochemistry about nitrogen that makes formation of positively charged nitrogen, as in (56), impossible.

The difference in the reactivity of 2-imidazolidinone (58) and 1,3-dimethylurea is quite strange. Steric crowding should be slight for (58) and we expected it to react with diacetyl and 1-phenylpropane-1,2-dione in the same way to give the diol (60), analogous to (37), which should then condense themselves to give products similar to (33) and (41). The fact that this does not occur is difficult to explain. The diol (60) is not particularly strained and so formation is not unfavourable. However, we have found that 2-imidazolidinone readily forms polymeric materials, which will be discussed in the next Chapter. The large ring in (59) may make its formation occur with an ease not possible in the reactions discussed above.



76

77

EXPERIMENTAL

a) Urea - A mixture of diacetyl (8.6 g) and urea (12.0 g) in benzene (50 ml) and TFA (5 ml) was refluxed for about 2 h at 90°. The water formed during the reaction was removed by azeotropic distillation. On completion, the contents of the flask were cooled down and an excess of methanol was added with constant stirring. A white solid, contaminated by a deep purple gum, settled out. It was filtered, the residue was washed with methanol and then water. It was recrystallised from hot DMSO and finally washed with acetone. When dried, it had m.p. 348°. 3a,7a-dimethyltetrahydro-imidazo(4,5-d)imidazole-2,5-dione (28a).

The same product was also obtained when a mixture of diacetyl and urea in ethanol saturated with HCl gas was allowed to stand overnight. The solid was filtered off and recrystallised as described above.

The azeotropic distillation technique as described above was used throughout.

b) A mixture of urea (3g) and 1-phenylpropane-1,2-dione (2 ml) was refluxed for 1 h. An excess of methanol was added to the contents of the flask and the precipitate filtered off. The material was dissolved in hot DMSO and brought out of solution by addition of methanol. After filtration the material was washed with acetone to give 3a-methyl-4a-phenyltetrahydroimidazol[4,5-d]imidazole-2,5-dione (28b).

After isolation of precipitate at the first stage the highly coloured methanol filtrate was reduced in volume and an excess of acetone added to it. A white solid settled out, washed with methanol and recrystallised as described above. When dried it had m.p. 310° 4,4'-methylenebis(5-phenyl-4-imidazolin-2-one) (33h).

c) 1-Methylurea - The reaction time for 1-methylurea (0.2 mole) and butane-2,3-dione (0.1 mole) was 2 h. After removal of benzene and TFA methanol was added to the residue and the white solid filtered off. The filtrate was deep orange. The solid was recrystallised from DMSO and washed with acetone to give a mixture of 1,4,3a,7a-tetramethyltetrahydroimidazo-(4,5-d)imidazole-2,5-dione (28c) and 1,6,3a,7a-tetramethyltetrahydroimidazo(4,5-d)-imidazole-2,5-dione (28d).

d) A mixture of 1-methylurea (3g) and 1-phenylpropane-1,2-dione (2 ml) was refluxed for 4 h. After keeping overnight unchanged 1-methylurea was filtered off and the benzene removed by evaporation. The residue was put onto an alumina column and eluted with chloroform. After removal of the solvent an orange liquid remained which deposited crystals by addition of acetone and standing. The material was recrystallised from methanol to give a mixture of 4,4'-methylenebis-(1-methyl-5-phenyl-4-imidazolin-2-one) (33a) and 4,4'-methylenebis-(3-methyl-5-phenyl-4-imidazolin-2-one (33b).

The vapours from the reaction mixture were passed thr ough a cold trap and then through baryta water, which turned milky. The

above preparation was repeated with the reactants at room temperature and allowed to stand overnight to see if we could isolate an intermediate before the loss of CO_2. The product was worked up in the same way as before and an identical product was obtained.

This reaction did not give any product like (28e) and (28f).

e) 1,3-Dimethylurea - Butane-2,3-dione (5 ml) and 1,3-dimethylurea (8.8 g) were allowed to react under reflux for 40 minutes, the benzene and TFA removed by evaporation, and the residue purified by elution from an alumina column (type H) with chloroform. Removal of chloroform left a gum which crystallised on standing and the product was recrystallised from methanol to give 4,4'-methylenebis(1,3,5-trimethyl-4-imidazolin-2-one) (33d).

CO_2 was precipitated as $BaCO_3$ when the reaction vapours were passed through baryta water.

f) The reaction time for 1-phenylpropane-1,2-dione (2 ml) and 1,3-dimethylurea (3 g) was 4 h. Benzene was removed by evaporation to leave a purple syrup. This was put onto an alumina column and eluted with chloroform. Removal of the solvent left an orange liquid which, on standing, deposited crystals. The crystals were washed with ethyl acetate and recrystallised from acetone to give 1,3-dimethyl-2-oxo-5-phenyltetrahydroimidazole-4-spiro-4'-(1',3'-dimethyltetrahydroimidazole-2'-one) (41).

g) The reaction time for 1,3-diethylurea was 1.5 h. The benzene was removed and the residue put onto an alumina column (type H) and eluted with ethyl acetate. Removal of the solvent left a yellow liquid and addition of ether produced a solid. The solid was filtered off and washed with ether to give crystals of 1,3-diethyl-2-oxo-5-phenyltetrahydroimidazole-4-spiro-4'-(1',3'-diethyltetrahydroimidazole-2'-one) (46).

h) The filtrate, after the removal of (28c-d), was reduced, cooled and diluted with acetone. A cream solid was obtained while any unreacted methylurea and diacetyl remained in acetone. It was filtered off, dissolved in methanol and neutralised with liquid ammonia. The solid was brought out by the addition of excess acetone. It was treated with methanol, NH_4Cl remained solid while the material responsible for colour went into methanol. On solvent evaporation and dilution with acetone gave (48a-b), filtered off under dry nitrogen or in complete vacuum.

i) Repetition of the isolation procedure described above yielded (48d) from the reaction of urea and butane-2,3-dione.

Effect of ions on diacetyl-urea reaction

i) a. Compound (33d) (200 mg) was dissolved in methanol (100 ml). Five test tubes were taken each containing 10 ml solution of (33d). In four test tubes, aqueous solutions of Na_2SO_4, Na_3PO_4, $FeSO_4$ and $FeCl_3$ were added, but the colour remained the same as in the fifth,

blank tube, even on keeping the solution overnight. However, on addition of acid, colour appeared immediately and intensified with the passage of time. This intensification was very rapid when air was blown through the solution. The addition of ascorbic acid, a radical trap, did not show any change.

i) b. Urea (25 mg) was dissolved in water (100 ml). One drop of diacetyl was added to 10 ml of this solution but no colour formation took place, even in the presence of the cations and anions mentioned above. But on adding conc. H_2SO_4, in the presence as well as in the absence of these ions, colour appeared. When normal water was replaced by deoxygenated water (N_2 gas was bubbled through water for 4 h) we observed the same effect as described above.

i) c. In another experiment, hydroquinone solution (dissolved in aqueous methanol) was added to the aqueous solution of urea (10 ml) containing a few drops of diacetyl. On adding conc. H_2SO_4, no coloration appeared. After half an hour a slightly yellow colour developed, but in blank experiment (without hydroquinone) there was an intense golden colour.

In all the above experiments, the intensity of yellow colour varied with the strength of acid.

i) d. Compound (28a) was dissolved in conc. H_2SO_4. On warming it gave golden coloration and the solution absorbed at the same wavelength as the solution resulting from diacetyl-urea reaction. Other compounds (28b-h) which are analogues of (28a) also exhibited the same effect.

j) Acetoin (5 ml), urea (3 g) and TFA (3 ml) were refluxed in benzene for 4 h. On cooling a white solid separated and the crystals of 4,5-dimethyl-4-imidazolin-2-one (50a) were washed with acetone, m.p. 290° (decomp.) (lit. 290° (dec.), Blitz, 1907).

k) The reaction time for 1-methylurea (3.78 g) and acetoin (5 ml) was 3 h. Benzene was removed and flask contents were put onto alumina column (type H) and eluted with chloroform. Removal of the solvent left a white solid contaminated with gum. It was removed with acetone and recrystallised from chloroform, gave 1,4,5-trimethyl-4-imidazolin-2-one (50b), m.p. 185°.

l) A similar reaction with propionoin and urea gave a gum on solvent evaporation. It was put onto alumina oxide column and eluted with chloroform and acetone. The acetone extraction on solvent removal gave a yellow liquid, from which a white solid was precipitated by the addition of an excess acetone. The solid, was washed with acetone and then ether, gave 4,5-diethyl-4-imidazolin-2-one (50c), m.p. 284°.

m) A mixture of phenylacetylcarbinol (2 ml) and urea (2 g) was refluxed for 3h with removal of water. After solvent evaporation, the flask contents were treated by column chromatography. Elution with methanol gave 4-methyl-5-phenyl-4-imidazolin-2-one (50d). After washing with water and ether, it had m.p. 290° (decomp.) (lit. 285° (dec), Behr-Bregowski, 1897).

n) Similarly, with 1-methylurea and phenylacetylcarbinol the product is 1,4-dimethyl-5-phenyl-4-imidazolin-2-one (50e), m.p. 170°.

p) Benzoin (4.25 g) and urea (3 g) in benzene (50 ml) and TFA (5 ml) were refluxed for 6 h at 90° with continuous removal of water. The solvent was stripped off, leaving behind a white solid which was washed with water, chloroform and finally with ether, 3a,7a-diphenyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (28 g), m.p. 352°.

q) Similarly, the reaction of benzoin and 1-methylurea gave a mixture of 1,6-dimethyl-3a,7a-diphenyltetrahydroimidazo[4,5-d]-imidazole-2,5-dione (28h) and 1-methyl-4,5-diphenyl-4-imidazolin-2-one (50f), m.p. 196° (not sharp).

Compound (28h) is a very minor product difficult to separate from (50f).

r) 1,5-Diphenyl-2,4-dihydroxypentane-1,5-dione (52). It was prepared by hydrolysis of 1,5-diphenyl-2,4-dibromopentane-1,5-dione (51). The dibromide was synthesised from 1,5-diphenylpentane-1,5-dione (Francis and Michie, 1901) by using the method of Cowper and Davidson (1939). The dibromide (12.3 g) and silver oxide (7.5 g) in 70% aqueous acetone were stirred at room temperature for 1 h and after that refluxed for two h. Silver oxide was filtered off and the acetone removed leaving behind a white solid in water. The white solid was filtered off, dissolved in acetone and allowed to stand for some time, and gave beautiful white crystals of 1,5-diphenyl-2,4-dihydroxypentane-1,5-dione (52), m.p. 144°. The filtrate on

solvent evaporation yielded a greenish yellow solid, after washing with ether and drying had m.p. 244°, 1,4-dibenzoyl-2H-oxete (53).

Reactions of cyclohexane-1,2-dione

s) With 1,3-dimethylurea - After refluxing for 3 h benzene was removed to leave a viscous liquid. This was purified by column chromatography (basic alumina) and eluted with acetonitrile and ethanol. The first eluant contai ned unreacted cyclohexane-1,2-dione, while the second, after removal of solvent, yielded a yellow liquid. A solution of this in ethanol was poured into petrol with vigorous stirring and a white precipitate formed. After filtration the material (55a) was washed with ether and dried.

For the spectral study of acid solutions of (55a) equal volumes of a 0.1 M aqueous solution of (55a) and aqueous HCl were mixed and the spectrum recorded immediately on a Unicam SP800 spectrophotometer. The concentration of the coloured species was measured by the absorbance of the solution at 580 nm in a cell of 1 mm path length. Acidity function data were those of Paul and Long (1957) (H_o) and Arnett and March (1966) (H_R).

t) With urea - The above procedure was repeated using urea in place of 1,3-dimethylurea. After refluxing for 2 h, the reaction mixture was cooled and a large volume of acetone added. The white precipitate was filtered off, washed with water, acetone and ether to give (55b) as white powder.

The filtrate was deep purple and addition of ether produced a violet solid. This appears to be a mixture and we were unable to characterise it with certainty. In the carbon-13 nmr spectrum there were peaks at δ 132.7, 137.5 and 149.2 ppm, in addition to sp^3 hybridised carbons and carbonyl carbons. This is consistent with formation of olefinic double bonds as in (57b).

u) With 2-imidazolidinone - After refluxing for 3 h the contents of the flask were cooled and petrol added with stirring. The solid which separated was filtered off and recrystallised from chloroform to give white crystals of (59).

v) Equal molar quantities of diacetyl and 2-imidazolidinone were refluxed for 5 h at 90°. Benzene was removed and the flask contents were cooled. It was treated with column chromatography (Al_2O_3) using ethanol as washing solvent. The ethanol extraction, after removal of solvent, was poured into ether with vigorous stirring. A light brownish solid settled out, washed with ether and dried under reduced pressure, gave a polymer.

Physical Data

a) 3a,7a-Dimethyltetrahydroimidazo(4,5-d)imidazole-2,5-dione (28a)

M.p. 348°, m/e 170 (M^+), ν_{max} 3240 (NH), 1720 and 1670 cm^{-1} (C=O), δH (TFA) 1.80 (6H, s) and 7.30 (2H, broad s), δC(TFA) 21.86 (q), 80.64 (s) and 164.10 (s) ppm. (Found: C, 42.34; H, 5.94; N, 32.93. $C_6H_{10}N_4O_2$ requires C, 42.41; H, 6.01; N, 32.73).

b) 3a-Methyl-4a-phenyltetrahydroimidazol[4,5-d]imidazole-2,5-dione (28b)

M.p. 348°, m/e 232 (M^+), ν_{max}(mull) 3220-3100 (NH), 1730 and 1680 cm^{-1} (C=O), δH ([$^2H_6$]DMSO, 110°), 0.8 (3H, s), 6.61 (1H, s), 6.93 (1H, s) and 7.36 (5H, s) ppm. δC(TFA) 23.96, 82.37, 85.07, 127.79, 131.04, 132.41, 135.31, 164.64, and 164.93 ppm. (Found: C, 57.00; H, 5.2; N, 24.15. $C_{11}H_{12}N_4O_2$ requires C, 56.95; H, 5.2; N, 24.15 .)

4,4'-Methylenebis(5-phenyl-4-imidazolin-2-one) (33h)

M.p. 310°, m/e 332 (M^+), ν_{max} 3320-3120 (NH), 1735 cm^{-1} (C=O), δH ([$^2H_6$]DMSO) 3.75 (2H, s), 7.25 (10H, s), 10.0 (2H, s), and 10.12 (2H, s) ppm. δC([$^2H_6$]DMSO) 20.72, 114.69, 118.13, 126.19, 126.41, 128.34, 129.81 and 154.02 ppm. (Found: C, 68.64; H, 4.79; N, 16.63. $C_{19}H_{16}N_4O_2$ requires C, 68.66; H, 4.85; N, 16.85%.)

c) 1,4,3à,7a-Tetramethyltetrahydroimidazo-(4,5-d)imidazole-2,5-dione (28c) and 1,6,3à,7a-tetramethyltetrahydroimidazo(4,5-d)-imidazole-2,5-dione (28d)

M.p. 305°, m/e 198 (M^+), ν_{max} 3290 (NH) and 1730 cm^{-1} (C=O) δ H ([$^2H_6$]DMSO, 100°) 1.39, 1.41, 1.49 (12H, 3s), 2.61 (3H, s), 2.78 (9H, s), 7.33 (3H, s) and 7.55 (1H, s) ppm. δC(TFA) 16.23, 19.09, 22.25, 26.25, 28.00, 78.56 (s), 82.34 (s), 86.62 (s), 162.78 (s) and 163.25 (s) ppm. (Found: C, 48.50, H, 7.30; N, 28.20 . $C_8H_{14}N_4O_2$ requires C, 48.47; H, 7.11; N. 28.26%.)

d) 4,4'-Methylenebis(1-methyl-5-phenyl-4-imidazolin-2-one (33a) and 4,4'-Methylenebis(3-methyl-5-phenyl-4-imidazolin-2-one) (33b)

M.p. 290° (decomp.), m/e 360 (M^+), ν_{max} (mull) 3155-3110 (NH), 1680 (C=O) and 1600 cm^{-1} (C=C), δ H([$^2H_6$]DMSO) 2.82 (6H, s), 4.04 (2H, s), and 7.30 (12H, s), δ C([$^2H_6$]DMSO) 19.66 (t), 26.63 (q), 114.80 (s), 118.10 (s), 126.79, 128.24, 129.74, and 153.13 (s) ppm. (Found: C, 69.79; H, 5.71; N, 15.08. $C_{21}H_{20}N_4O_2$ requires C, 69.98; H, 5.59; N, 15.54%)

e) 4,4'-Methylenebis(1,3,5-trimethyl-4-imidazolin-2-one) (33d)

M.p. 218°, m/e 264 (M^+), ν_{max} (mull) 1690 (C=O) and 1660 cm^{-1} (C=C), δH($CDCl_3$) 1.99 (6H, s), 3.09 (6H, s), 3.17 (6H, s) and 3.58 (2H, s), δC($CDCl_3$) 8.41 (q), 19.00 (t), 27.35 (q), 112.60 (s), 115.03 (s), and 153.53 (s) ppm (Found: C, 59.05; H, 7.95; N, 21.30 $C_{13}H_{20}N_4O_2$ requires C, 59.07; H, 7.62; N, 21.19%)

f) 1,3-Dimethyl-2-oxo-5-phenyltetrahydroimidazole-4-spiro-4'-(1',3'-dimethyltetrahydroimidazole-2'-one) (41)

M.p. 148°, m/e 288 (M^+), ν_{max} (mull) 1710 cm^{-1} (C=O), δH($CDCl_3$) 2.65-2.79 (14H, unresolved singlets), 4.53 (1H, s) and 7.16-7.46 (5H, m) ppm. δC($CDCl_3$) 24.58, 24.70, 28.27, 29.90, 50.54, 66.49, 77.89, 127.13, 128.71, 134.35, and 158.51 ppm. The shift at 77.89 ppm was observed when [$^2H_6$]acetone was used as the solvent. In this solvent the other shifts show very slight changes from those quoted. (Found: C, 62.4; H, 7.05; N, 19.4 $C_{15}H_{20}N_4O_2$ requires C, 62.5; H, 7.0; N, 19.45%)

g) 1,3-Diethyl-2-oxo-5-phenyltetrahydroimidazole-4-spiro-4'-(1',3'-diethyltetrahydroimidazole-2'-one) (46)

M.p. 114°, m/e 344 (M^+), ν_{max} (mull) 1710 cm^{-1} (C=O), δH ($CDCl_3$) 0.86-1.34 (12H, m), 2.5-3.5 (8H, m), 3.71 (2H, dd, J 8 Hz) 4.56 (1H, s) and 7.14-7.44 (5H, m), δC($CDCl_3$) 12.56, 12.80, 15.35, 34.71, 35.99, 37.96, 49.61, 65.86, 78.90, 127.75, 129.15, 135.44, and 158.74 ppm (Found: C, 66.2; H, 8.5; N, 16.0 $C_{19}H_{28}N_4O_2$ requires C, 66.25, H, 8.2; N, 16.25%)

j) 4,5-Dimethyl-4-imidazolin-2-one (50a)

M.p. 290° (decomp.) (lit. 290° (decomp.), Blitz, 1907), m/e 112 (M^+), ν_{max} (mull) 3130 (NH), 1685 (C=O), and 1665 cm^{-1} (C=C), δH(TFA) 2.14 (6H, s) and 9.96 (1H, s), δC(TFA) 8.7 (q), 119.5 (s), and 151.2 (s) ppm. (Found: C, 53.58; H, 7.66; N, 25.96 $C_5H_8N_2O$ requires C, 53.55; H, 7.19; N, 25.09%)

k) 1,4,5-Trimethyl-4-imidazolin-2-one (50b)

M.p. 185°, m/e 126 (M^+) ν_{max} (mull) 3150 (NH), 1685 (C=O) and 1650 cm^{-1} (C=C), δH ($CDCl_3$) 1.94, 1.98 (6H, 2s), 3.12 (3H, s), and 11.49 (1H, s),

δC($CDCl_3$) 8.3, 9.20, 26.9 (q), 112.2 (s), 113.8 (s), and 154.6 (s) ppm (Found: C, 56.4; H, 7.85; N, 22.31. $C_6H_{10}N_2O$ requires C, 57.12; H, 7.98; N, 22.20%)

l) 4,5-Diethyl-4-imidazolin-2-one (50c)

M.p. 284°, m/e 140 (M^+), ν_{max} (mull) 3140 (NH), 1690 (C=O) and 1670 cm^{-1} (C=C), δH([$^2H_6$]DMSO) 1.02 (6H, t, J 8Hz), 2.22 (4H, q, J 8Hz), 8.52 (1H, s), and 9.50 (1H, s), δC(TFA) 13.9 (q), 18.3 (t), 125.3 (s) and 151.2 (s) ppm (Found: C, 59.71; H, 8.64; N, 19.54 $C_7H_{12}N_2O$ requires C, 59.97; H, 8.62; N, 19.98%)

m) 4-Methyl-5-phenyl-4-imidazolin-2-one (50d)

M.p. 290° (dec.) (lit. 285°, Behr-Bregowski, 1897), m/e 174 (M^+) ν_{max} (mull) 3180 (NH) , 1690 (C=O) and 1650 cm^{-1} (C=C) δH(TFA) 2.36 (3H, s) and 7.42 (5H,) δC(TFA) 10.2, 82.6, 85.3, 127.9-132.6, 137.2 and 161.6 ppm.

n) 1,4-Dimethyl-5-phenyl-4-imidazolin-2-one (50e)

M.p. 170°, m/e 188 (M^+), ν_{max} (mull) 3460 (NH) , 1690 (C=O), and 1675 cm^{-1} (C=C), δH ([$^2H_6$]DMSO) 0.78 (3H, s), 2.48 (3H, s), 7.18-7.32 (5H, m) and 5.90 (1H, s) ppm. δC ([$^2H_6$]DMSO) 24.4, 24.8, 85.6, 91.9, 126.7, 127.95, 128.1, 139.0 and 158.7 ppm (Found: C, 69.96; H, 6.34; N, 14.72 $C_{11}H_{12}N_2O$ requires

C, 70.19; H, 6.41; N, 14.88%)

p) 3a,7a-Diphenyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (28g)

M.p. 352°, m/e 147 ($M^+/2$). ν_{max} (mull) 3190 (NH) and 1675 cm^{-1} (C=O) δ H(TFA) 7.13 (10H, s) and 7.57 (4H, s) ppm, δC(TFA) 87.03, 128.03, 130.36, 131.75, 135.31 and 165.78 ppm

q) 1,6-Dimethyl-3a,7a-diphenyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (28h) (very minor product), and 1-Methyl-4,5-diphenyl-4-imidazolin-2-one (50f). It is a mixture.

M.p. 196° (not sharp), m/e 250 and 322 (M^+), δH[$^2H_4$]acetic acid 0.6 (3H, s), 2.96 (6H, s), 3.14 (6H, s), 7.08-7.54 (aromatic protons) and 7.82 (s) ppm. δC(TFA) 123.85, 127.28, 127.63, 128.08, 129.14, 130.28, 130.87, 131.82, 139.31, and 160.0 ppm (Found: C, 74.94; H, 4.36; N, 7.56 $C_{16}H_{14}N_2O$ requires C, 76.77; H, 5.63; N, 11.19%) It decolorised bromine solution.

r)a. 1,5-Diphenyl-2,4-dibromopentane-1,5-dione (51)

It is a racemic misture, m.p. 90°, after recrystallisation from ether, m.p. 114°, m/e 250 (M^+-2HBr), ν_{max} (mull) 1680 cm^{-1} (C=O) δH($CDCl_3$) 2.98 (2H, m), 5.54 (2H, m), 7.43-8.04 (10H, m) ppm δC($CDCl_3$) 36.58, 45.80, 128.82, 133.92 and 191.91 ppm (Found: C, 49.89; H, 3.42. $C_{17}H_{14}Br_2O_2$ requires C, 49.80; H, 3.41%)

r)b. 1,5-Diphenyl-2,4-dihydroxypentane-1,5-dione (52)

M.p. 144°, m/e 267 (M^+-OH, ν_{max} (mull) 3510 (OH) and 1685 cm^{-1} (C=O), δH($CDCl_3$) 1.88 (2H, m), 3.92 (2H, s), 5.62 (2H, m),

7.40-7.98 (10H, m) ppm, the peak at 3.92 ppm disappeared with addition of D_2O, $\delta C([^2H_6]DMSO)$ 39.24, 69.55, 128.46, 128.72, 133.26, 134.69, and 201.03 ppm; (Found: C, 71.53; H, 5.55 $C_{17}H_{16}O_4$ requires C, 71.81; H, 5.67%). It is a racemic mixture.

r)c. 2,4-Dibenzoyl-2H-oxete (53)

M.p. 244°, m/e 264 (M^+), ν_{max} (mull) 1640 and 1590 cm^{-1} (C=O) $\delta H([^2H_6]DMSO)$ 7.15 (1H, s), 7.37-8.07 (10H, m), 10.27 (1H, s) ppm $\delta C([^2H_6]DMSO)$ 115.18, 123.78, 127.34, 128.57, 128.91, 129.74, 132.43, 137.15, 139.78, 143.69, 147.22, 180.81 ppm. (Found: C, 76.97; H, 4.37 . $C_{17}H_{12}O_3$ requires C, 77.26; H, 4.57%) It decolorised $KMnO_4$ solution.

s) Compound (55a)

Decomposition (ie. loss of water) commenced at ca. 164°, m/e 328 (M^+-4H_2O), ν_{max} 3500-3100 (OH) and 1700-1640 cm^{-1} (C=O) $\delta H(CDCl_3)$ 1.82 (8H, broad s), 2.30 (8H, broad s), 2.76-3.77 (12H, unresolved ss), $\delta C(CHCl_3)$ 18.3, 19.7, 27.3-30.9, 58.0, 153.7, and 153.9 ppm (Found: C, 55.9; H, 6.4; N, 14.6 $C_{18}H_{32}N_4O_6$ requires C, 54.0; H, 8.05; N, 14.0%). The material is damp and requires drying before analysis. During the drying it is difficult to avoid some elimination of water. This explains the poor analysis and, particularly, the low hydrogen content. However, the C:N ratio 9:2 is correct for (55a).

t) Compound (55b)

M.p. 326° (dec.), ν_{max} 3240 (NH/OH), 1710 and 1615 cm^{-1} (C=O),

δH(TFA) 1.74 (8H, s), 2.18 (8H, s), 7.2 (v. broad s), δC(TFA) 17.6, 31.8, 79.4 and 165.5 ppm (Found: C, 48.89; H, 6.45; N, 16.73 $C_{14}H_{24}N_4O_6$ requires C, 48.83; H, 7.02; N, 16.27%)

u) Compound (59)

M.p. 180° (dec.), m/e 274 (M^+-$2H_2O(CH_2NH)_2CO$), ν_{max} 3140-3400 (OH) and 1650-1710 cm^{-1} (C=O), δH($CDCl_3$ 2.0-2.4 (16H, 2s), 3.45 (8H, s), 4.2-4.5 (4H, s), δC($CHCl_3$) 21.7-29.3, 37.7-40.6, 52.5, 62.3, 158.9, 159.7 and 160.1 ppm (Found: C, 53.1; H, 6.05; N, 13.3 $C_{18}H_{28}N_4O_6$ requires C, 54.5; H, 7.1; N, 14.1%) The problems associated with elemental analysis, described previously, apply here. The C:N ratio is 9:2.

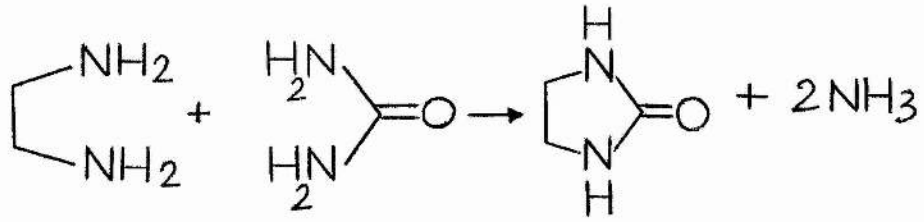
CHAPTER 3

Reaction of urea, 1-methylurea, 1,1'-dimethylurea and 1,3-dimethylurea with 1,2-diaminoethane, 1,2-dimethylaminoethane, 1-dimethylamino-2-aminoethane and, 1,3-diaminopropane.

INTRODUCTION

Besides mono and diketones, urea also reacts with diaminoethane and its N-alkyl derivatives to yield 2-imidazolidinones, often known as ethyleneurea derivatives. The imidazole ring system exists in many substances of biological and chemical interest, both natural and synthetic. The widespread application of 2-imidazolidinone, its N-alkyl derivatives and other related compounds in the field of textile, medicine, detergents, adhesives and, as industrial solvents has prompted us to look into reaction mechanism in the formation of such important compounds. We have found that it is the carbon-nitrogen bond of urea which breaks down during the formation of products. This has been further confirmed by the use of isotopic labelling technique, physical, chemical and spectral methods. First, an isocyanate intermediate is formed which gives birth to a polymer. This polymer on heating changes to a monomer.

This chapter deals with the reaction of urea, 1-methylurea, 1,1'-dimethylurea and 1,3-dimethylurea with 1,2-diaminoethane, 1,2-dimethylaminoethane, 1-dimethylamino-2-aminoethane and, finally, with 1,3-diaminopropane.



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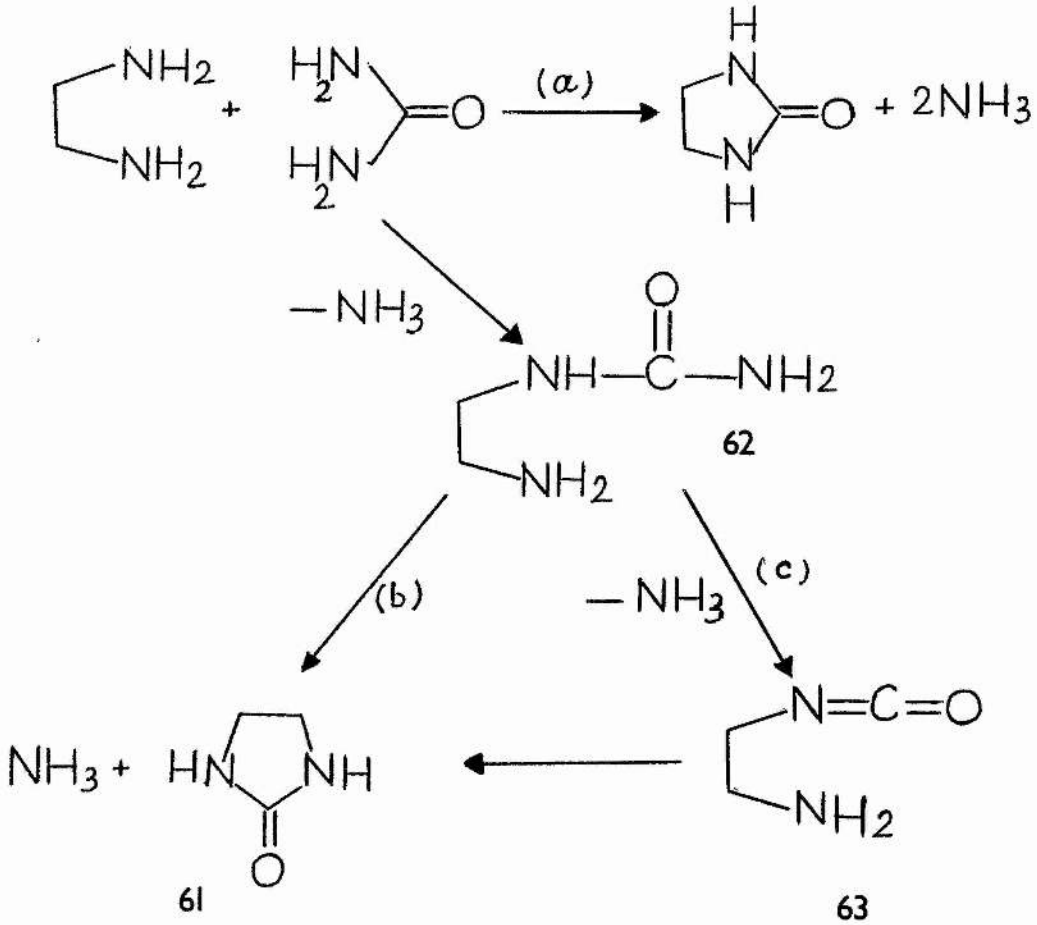
SCHEME 12



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SCHEME 13

RESULTS AND DISCUSSION

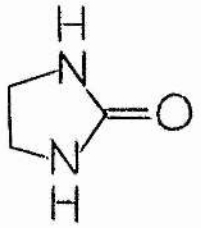
The preparation of 2-imidazolidinone (61) was first reported by Hansen (1939) but a yield of only 10% was obtained. However, Schweitzer (1950) discovered that, if water is added, the yield increases to 98%. It has also been synthesised by reactions of several substances with 1,2-diaminoethane, ie. diethyl carbonate (Tafel and Reindle, 1901), phosgene (Puschin and Mitic, 1937) and urea as shown in Scheme 12 . The ammonia liberated by this reaction could come either from the urea or from the diaminoethane. When the urea used was labelled with nitrogen-15 we found none of this isotope in the 2-imidazolidinone formed. However, the ammonia evolved, which was trapped as ammonium chloride, did contain nitrogen-15. Thus, it is the carbon-nitrogen of urea which is broken during the course of the reaction.

There are several possible mechanisms for this reaction, the most probable are given in Scheme 13.

a) Reaction occurs by concerted elimination of two molecules of ammonia in a single step process.

b) Formation of the intermediate (62) is followed by intramolecular nucleophilic attack on the carbonyl group, with elimination of ammonia.

c) Intermediate (62) is converted into an isocyanate (63) with loss of ammonia, and subsequent cyclisation of (63) gives (61). Similar considerations have been applied by Hegarty and Frost (1973) to the hydrolysis of p-nitrophenyl-N-phenyl-carbamate and the conversion of p-nitrophenyl-N-(2-aminophenyl)carbamate into o-phenylenurea. They found evidence for the intermediacy of an



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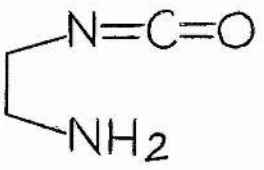

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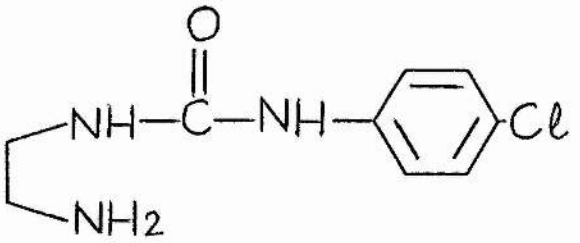

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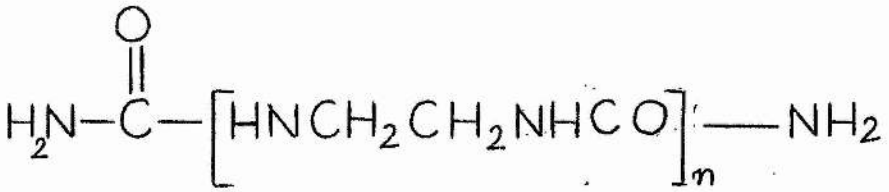

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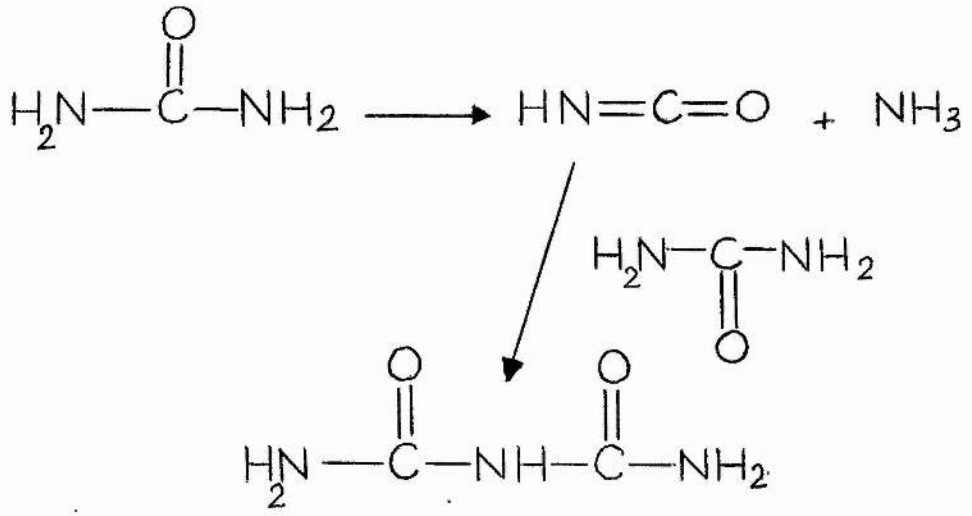
isocyanate and so, a priori, (c) is the favoured route.

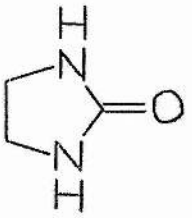
Hegarty and Frost (1973) trapped an isocyanate intermediate in the hydrolysis of p-nitrophenyl-N-phenylcarbamate by reaction in the presence of p-chloroaniline and isolated N-phenyl-N'-(p-chlorophenylurea). We carried out a similar experiment by heating a mixture of urea, diaminoethane, water, and p-chloroaniline but the last of these was recovered unchanged, and we found no trace of (64), which could have been formed by reaction of (63) with p-chloroaniline. However, this negative result does not disprove the intermediacy of (63) as intramolecular reaction, to form (61), may well proceed more readily than intermolecular reaction with p-chloroaniline.

Water does not appear to play a chemical role in the reaction and acts only as a moderator. We tried toluene in place of water. Reaction does occur, as evidenced by the ammonia evolved, but the solid product appears to be a polymer, probably of the linear type (65). If n is large then the elemental analysis of (65) is almost the same as that of (61). Also, many of the spectral properties will be identical. However, the melting point of the product (191^{o}) is very different from that of (61) (130^{o}). Although the main fragment in the mass spectrum is at m/e 86,(M^{+}) for (61), there are many smaller peaks of higher m/e. The appearance of the spectrum is characteristic of a polymer. It would appear, then, that water is a specific moderator for the formation of (61).

As both carbon-nitrogen bonds of the urea are broken during reaction, 2-imidazolidinone (61) should be obtained by reaction of 1-methylurea, 1,1-dimethylurea, and 1,3-dimethylurea with



SCHEME 14



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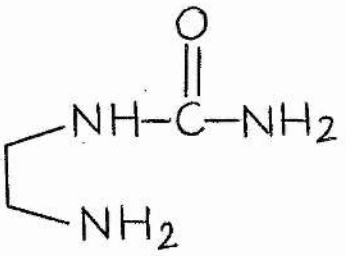

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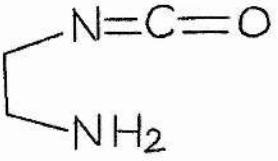

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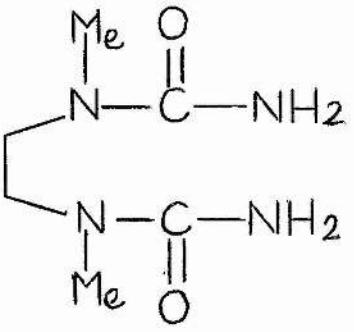
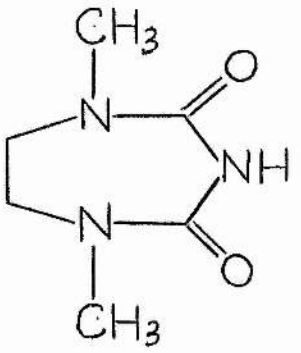


66

1,2-diaminoethane. This was found to be the case with the first two but, instead of (61), polymeric material was obtained although the experimental conditions were the same as those which produced the monomer on reaction with urea. There was no evidence, in the proton nmr spectra of the polymers, for the presence of N-methyl groups. The gases evolved during reaction were methylamine and dimethylamine, along with ammonia.

No reaction occurred with 1,3-dimethylurea and this suggests that formation of the intermediate (62) is blocked. With urea formation of (62) must parallel the biuret reaction (Wiedemann, 1848), where diaminoethane replaces the second mole of urea (Scheme 14). 1,3-Dimethylurea does not appear to undergo a simple biuret reaction and 1,5-dimethylbiuret is made by the reaction of 1-methylurea with methyl isocyanate (Biltz and Jeltsch, 1923). Therefore, 1,3-dimethylurea does not react with diaminoethane in a manner parallel to that shown in Scheme 14 and is recovered unchanged from the reaction mixture.

We now consider the effect of N-methylation of the diamine upon course of the reaction. The isocyanate intermediate (63) cannot form from 1,2-dimethylaminoethane and so reaction with urea should give a different type of product. In fact, (66) was obtained. Elemental analysis and molecular weight determination of (66) gave a molecular formula of $C_6H_{14}N_4O_2$, which corresponds to reaction of one mole of 1,2-dimethylaminoethane with two moles of urea and elimination of two moles of ammonia. The ir spectrum is consistent with the presence of NH and amide carbonyl groups. The proton nmr spectrum showed two singlets at δ 3.2 (6H) and



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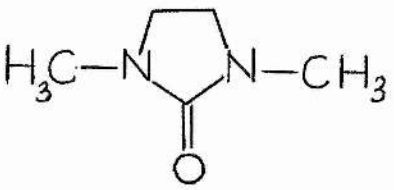
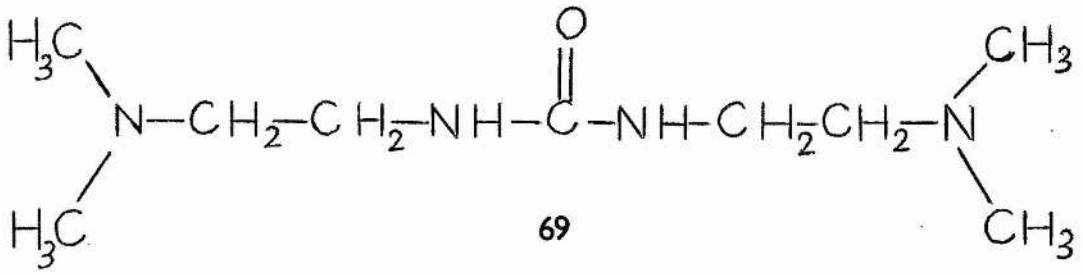


68

3.8 (4H) ppm which reflects the presence of N-methyl and methylene groups. The NH protons have exchanged with solvent (TFA). In addition to N-methyl and methylene groups at δ 36.62 and 48.77 ppm the carbon-13 nmr spectrum also gave a carbonyl peak at 162.36 ppm. Reaction with nitrous acid (which gave CO_2) and alkaline hydrolysis (which gave NH_3) confirms the existence of amide groups. This result is inconsistent with routes (a) and (b) (Scheme 13), but supports formation of an isocyanate intermediate.

However, our result appears to be inconsistent with the work of Lien and his co-workers (1971) who obtained 1,3-dialkyl-2-imidazolidinones by reaction of 1,2-dialkylaminoethanes with urea. The experimental conditions they used were very similar to ours, except that they used no moderator and heated for a longer period. We were able to resolve this inconsistency. The action of heat (ca. 300°) on (66) resulted in formation of a paste, most of which was soluble in chloroform, and the evolution of ammonia. On cooling the solution, white crystals were deposited which we identified, by spectral means, as the cyclic biuret (67). Removal of solvent from the filtrate left an oil, 1,3-dimethyl-2-imidazolidinone (68) (Boon, 1947), which is the product expected from Lien's work. The material insoluble in chloroform was cyanuric acid. It was identified by carbon-13 nmr spectrum and by comparison with an authentic sample. Thus it would appear that bisureas like (66) are intermediate in Lien's synthesis of dialkyl-2-imidazolidinones. What is not clear is whether (66) decomposes into (67) and (68) concurrently, or to (67) first, which reacts further to give (68). We favour the latter as conversion of (66) into (68) involves the



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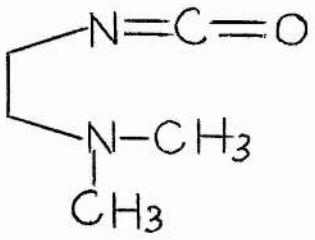

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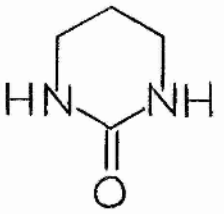
simultaneously elimination of ammonia and cyanic acid while, if reaction proceeds with the intermediacy of (67), these processes occur in a step-wise manner. The fact that (67) can be isolated supports this view.

The same product (66) was obtained by reaction of 1,2-dimethylaminoethane with 1-methylurea and with 1,1-dimethylurea. With 1,3-dimethylurea there was no reaction.

Reaction of 1-dimethylamino-2-aminoethane with urea gave yet another type of product, an N-substituted urea (69). We can readily rationalise this as cyclisation of the isocyanate intermediate (70) is not possible, and so it reacts with a second molecule of the diamine to give (69). This is further evidence to support the isocyanate intermediate. Compound (69) is a colourless liquid and, fragmented into two pieces at m/e 115 ($Me_2NCH_2CH_2NHCO$) and 87 ($MeNCH_2CH_2NH$) in the mass spectrum. However, elemental analysis corresponds to a molecular formula $C_9H_{22}N_4O$. The ir spectrum is in agreement with NH and amide carbonyl groups. The proton nmr spectrum exhibits one singlet (δ 2.18 ppm), two triplets (δ 2.40 and 6.52 ppm) and a quartet at δ 3.23 ppm. Addition of a few drops of D_2O resulted in disappearance of triplet at δ 6.52 and the quartet at 3.23 ppm changed into a triplet. The relative peak areas are consistent with number of protons 12, 4, 4 and 2 present in (69). The carbon-13 nmr spectrum shows four resonances at δ 37.71, 45.03, 58.99 and 160.52 ppm; which are concordant with the structure of (69), 1,3-bis(dimethylaminoethyl)urea.



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We found that a parallel reaction occurs when 1,2-diaminoethane was replaced by 1,3-diaminopropane. The solid products obtained on reaction with urea and with 1-methylurea was a mixture of (71) and polymeric material. Compound (71) was extracted with chloroform and identified by all means.

EXPERIMENTAL

Reaction of urea and 1,2-diaminoethane

A mixture of urea (0.1 mole), diaminoethane (0.1 mole) and water (0.2 mole) was refluxed for 3 h and the gas evolved passed into aqueous HCl. After 3 h the mixture became a paste but, during the next hour, turned into a pale liquid and, on cooling, solidified. The material was recrystallised from chloroform to give 2-imidazolidinone (61), m.p. 130° (lit. 131°; Fischer and Koch, 1885), m/e 86 (M^+), δ_H(TFA) 3.64, δ_C (H_2O) 43.4 and 164.4 ppm. Ammonium chloride was isolated from the solution through which the evolved gas had passed.

The above experiment was repeated using urea containing 3% nitrogen-15. The mass spectrum of the 2-imidazolidinone obtained was identical with that obtained above but in the mass spectrum of the ammonium chloride isolated there was a peak at m/e 29 (^{14}N-^{15}N) which is not found in isotopically normal ammonium chloride.

When toluene was used as the moderator a material was obtained m.p. 192°, the spectral properties of which were identical with those of (61), except that the mass spectrum had only a small peak at m/e 86 and many small peaks at higher values.

The first experiment described above was repeated using 1-methylurea instead of urea. The product had the following properties: m.p. 280° (dec.), m/e 86 (large) and small peaks at higher values, ν_{max} (mull) 3340 (NH) and 1650-1550 cm^{-1} (C=O, broad). δ_H (TFA) 3.58, δ_C(TFA) 42.5, 42.8 and 163.6 ppm.

(Found: C, 41.0; H, 7.1; N, 32.3 $(C_3H_6N_2O)_n$ requires C, 41.9; H, 7.0; N, 32.5%.) The material appears to be a polymer of (61).

With 1,1-dimethylurea another product (also a polymer) was obtained, m.p. 184°, m/e 86 (M^+) (large) and small peaks at higher values, ν_{max} (mull) 3430, 3340 (NH) and 1650 cm^{-1} (C=O), $\delta_{H(TFA)}$ 3.63 ppm.

Reaction of urea with 1,2-dimethylaminoethane

A mixture of dimethylaminoethane (0.1 mole), urea (0.1 mole) and water (0.2 mole) was refluxed for 4 h with constant stirring on a hot plate. At the end of approximately 2 h, the flask contents changed into white solid which remained as such throughout the heating. The solid product was washed with chloroform, acetone and water . When dried it had m.p. 262°, 1,1-dimethyl-1,1'-dimethylene-bisurea (66), m/e 174 (M^+), ν_{max} (mull) 3400, 3190 (NH) and 1655 cm^{-1} (C=O), δ_H (TFA) 3.20 (6H, s) and 3.80 (4H, s), $\delta_{C(TFA)}$ 36.6 (q), 48.8 (t) and 162.4 (s) ppm. (Found: C, 41.32; H, 8.64; N, 32.98 $C_6H_{14}N_4O_2$ requires C, 41.36; H, 8.10; N, 32.16%) The same product was obtained when urea was replaced by 1-methylurea or 1,1-dimethylurea.

a) Compound (66) was dissolved in hydrochloric acid and 10% aqueous solution of sodium nitrite was added into it. During addition the temperature was maintained at 0°C. The liberated gas was passed through byrta water and barium carbonate was obtained.

b) A mixture of compound (66) and aqueous solution of sodium hydroxide was heated. The ammonia evolved was identified as

ammonium chloride and with Nessler's reagent.

c) 1,1-Dimethyl-1,1-dimethylenebisurea (10.0 g) in a round bottom flask fitted with a water condenser was heated. The flask contents melted and ammonia started coming off. When it ceased the flask was cooled down and material was extracted with chloroform. On solvent removal and cooling the residue yielded beautiful white crystals of 1,5-dimethyl-1,5-dimethylenebisuret (67), m.p. 190°, m/e 157 (M^+), δH ([$^2H_6$]DMSO) 2.87 (6H, s), 3.45 (4H, s), 8.25 (1H, s) ppm; (Found: C, 45.83; H, 6.92; N, 26.48 $C_6H_{11}N_3O_2$ requires C, 45.85; H, 7.05; N, 26.73%)

After complete removal of (67), the other product of the reaction was a yellow liquid 1,3-dimethyl-2-imidazolidinone (68), m/e 114 (M^+), δH ($CDCl_3$) 2.75 (6H, s), 3.27 (4H, s), δC($CHCl_3$) 29.5, 43.3 and 160.1 ppm.

Reaction of urea with 1-dimethylamino-2-aminoethane

A mixture of the diamine (0.1 mole), urea (0.1 mole) and water (0.2 mole) was refluxed for 4 h. The ammonia evolved was passed into aqueous HCl and recovered as NH_4Cl. The contents of the flask were cooled, diluted with chloroform, and filtered. The solvents were removed and the residue dried (molecular sieve) to give a colourless, viscous oil, 1,3-bis-(dimethylaminoethyl)urea (69), m/e 87 ($Me_2NCH_2CH_2NH$) and 115 ($Me_2NCH_2CH_2NHCO$), ν_{max} (mull) 3330 (NH) and 1660 cm^{-1} (C=O). δH ($CDCl_3$) 2.18 (12H, s), 2.40 (4H, t), 3.23 (4H, q), 6.52 (2H, t), (addition of D_2O resulted in the disappearance of triplet at δ 6.52 and the quartet at 3.23 ppm changed into a triplet;

δ_C ($CHCl_3$) 37.7, 45.0, 54.0 and 160.5 ppm (Found: C, 53.35; H, 11.13; N 27.72 $C_4H_{22}N_4O$ requires C, 53.44; H, 10.96; N 27.70%)

Reaction of 1,3-diaminopropane with urea

The normal procedure was repeated using 1,3-diaminopropane. Acetone was added to the product and insoluble material filtered off. This material was extracted with chloroform and, on removal of solvent, gave trimethyleneurea (71), m.p. 262° (lit. 260°; Fischer and Koch, 1885), m/e 100 (M^+), ν_{max} (mull) 3240 (NH) and 1680 cm^{-1} (C=O), δ_H ($CDCl_3$) 1.83 (2H, m) and 3.23 (4H, t), δ_C(H_2O) 21.1, 40.3 and 159.6 ppm. The material insoluble in chloroform was polymeric.

CHAPTER 4

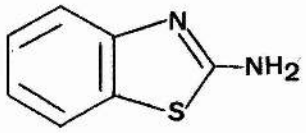
Oxidation of N-substituted thioureas with hydrogen peroxide, nitrous acid, bromine and benzoyl peroxide. Effect of base on Hector's Base adducts and nitration of Hector's Base.

INTRODUCTION

Oxidation of N-substituted thioureas with various oxidants yields a 1,2,4-thiadiazolidine ring system. The sensitivity of this ring to acid depends upon the positions of peripheral substituents. For example, with four phenyl groups, ie. 2,4-diphenyl-3,5-bis(phenylimin)-1,2,4-thiadiazolidine, acid catalysed rearrangement is rapid but, if two are replaced by methyl groups ie. 2,4-dimethyl-3,5-bis(phenylimin)-1,2,4-thiadiazolidine, then the reaction occurs much less readily. The product in both cases is a Hugerschoff's Base. On the other hand, we have found that Hector's Base (3-anilino-5-imino-4-phenyl-Δ^2-1,2,4-thiadiazolidine) and Dost's Base (3,5-dianilino-1,2,4-thiadiazole) and their methylated derivatives do not undergo rearrangement because of their conversion into heteroaromatic cations in acid solution. The cleavage of N-S bond in these cations appears to be impossible in view of the aromaticity lost. We have also proposed a reaction mechanism pertaining to the formation of thiadiazole ring and Hugerschoff's Base. In the former case, it is the amidinothiourea which gives birth to 1,2,4-thiadiazolidine ring system and N-alkyl or aryl substituted -α,α'-thiobisformamidine, which is a side product, has nothing to do with it. In the latter case, the protonation of the 1,2,4-thiadiazolidine at N(2) and fission of the N-S bond generate a sulphenium ion which undergoes electrophilic substitution to give the final product ie. Hugerschoff's Base.

Reaction of Hector's Base adducts resulting from carbon disulphide and phenyl isothiocyanate with sodium hydroxide in methanol/DMF solution gives another ring containing S-S bond ie. dithiazole ring. Two other adducts of Hector's Base with methyl isothiocyanate and phenyl isocyanate have been examined. The former reacts with sodium hydroxide with elimination of sulphur while the latter does not. Their reaction mechanism has also been proposed.

We have found that nitration of Hector's Base gives both mono and dinitro products. In each case, only one out of two phenyl rings involves in the nitration process and that ring is the 3-anilino portion of the Hector's Base. The protonation of the exocyclic nitrogen of Hector's Base seems to deactivate the phenyl ring attached to nitrogen at position 4, which in turn, does not react with ni tronium ion. Finally, acetylation of nitro compounds of Hector's Base and nitration of Hector's Base in acetylating mixture have also been discussed.



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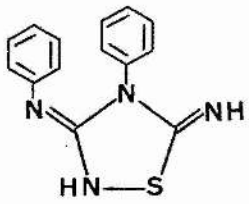

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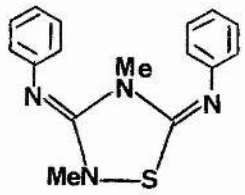

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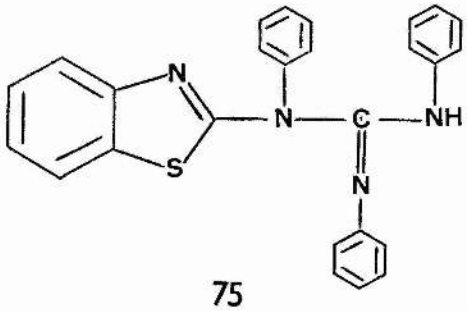

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RESULTS AND DISCUSSION

The oxidation of thioureas is a difficult matter. The product of reaction depends upon the oxidant, the molar proportion of reactants, the solvents, and the degree of N-substitution of the thiourea. A few examples will illustrate the diversity of reaction. Aminobenzothiazole (72) results from the reaction of 1-phenylthiourea with bromine in chloroform and this is a well known synthetic route to this compound as well as its N alkyl and aryl derivatives (Hugerschoff, 1903 and Elderfield, 1957). It has been shown that cyclisation of furylthioureas (Grehn and Lindberg, 1977), pyrrolylthioureas (Grehn, 1979) and 1-acyl-3-(3-thienyl)-2-thioureas (Grehn, 1978) may be effected in a similar way. On the other hand, oxidation of 1-phenylthiourea by hydrogen peroxide in ethanol gives Hector's Base (Hector, 1889), until recently thought to have structure (73). Oxidation of 1-methyl-3-phenylthiourea by nitrous acid in the same solvents gives the related compound (74) (Christophersen et al 1975), but one of the phenyl groups has a different position in the molecule. Again, treatment of 1,3-diphenylthiourea with bromine in chloroform gives, as the isolable product (75) (Hugerschoff, 1903). Compounds of this type are known as Hugerschoff's Bases and the evidence for the structural assignment will be discussed later. We thought it would be of interest to study systematically the variation of product with oxidant and with experimental conditions, and to seek a single reaction mechanism which explains the results.

Previous discussions of this matter have been complicated by uncertainty in the structure of the reaction products, particularly Hector's Base (Kurzer, 1965 and Joshua et al, 1961). Over the years, since Hector first reported isolation of the compound that bears his name, various structures have been suggested and (73) has found greatest favour (Kurzer, 1965). Christophersen et al (1975) attempted a definitive structure determination by preparing (74) and ascertained its crystal structure by X-ray analysis. This, they claimed, is an analogue of a 1,2,4-thiadiazole related to Hector's Base, known as Dost's Base (Dost, 1906). The latter is a rearrangement product of Hector's Base, made by heating Hector's Base with ethanolic ammonia in a sealed tube. These authors claimed that, having established the structure of (74), a Dost-type Base, then the base-catalysed rearrangement by which Dost's Base is made from Hector's Base leads to an unambiguous structure assignment for the latter. The weak links in the argument are obvious.

We approached the problem more directly in a manner which will be discussed thoroughly in the next chapter. Here, we mention a few points of interest. The structure of Hector's Base is (76) which differs from (73) only in the positions of a hydrogen and a double bond. A study of the nitrogen-15 nmr spectra of Hector's Base and related compounds has shown that this particular arrangement persists in solution. Moreover, Glidewell et al (1978) confirmed the structure of Hector's Base by X-ray method. In view of the information now available, previous discussions of the structure of Hector's Base will not be reviewed.

Similarly, carbon-13 and nitrogen-15 nmr spectra have shown, without doubt, that (77) is the correct structure in solution. There seems to be a general principle with compounds of this type that, if possible, the double bonds are in the ring rather than exocyclic. Dosts' Base is not an analogue of compound (74) for which Christophersen et al (1975) obtained a crystal structure. In (74) the N-methyl groups force the double bonds to be exocyclic. This difference, as we shall see later, is of some importance.

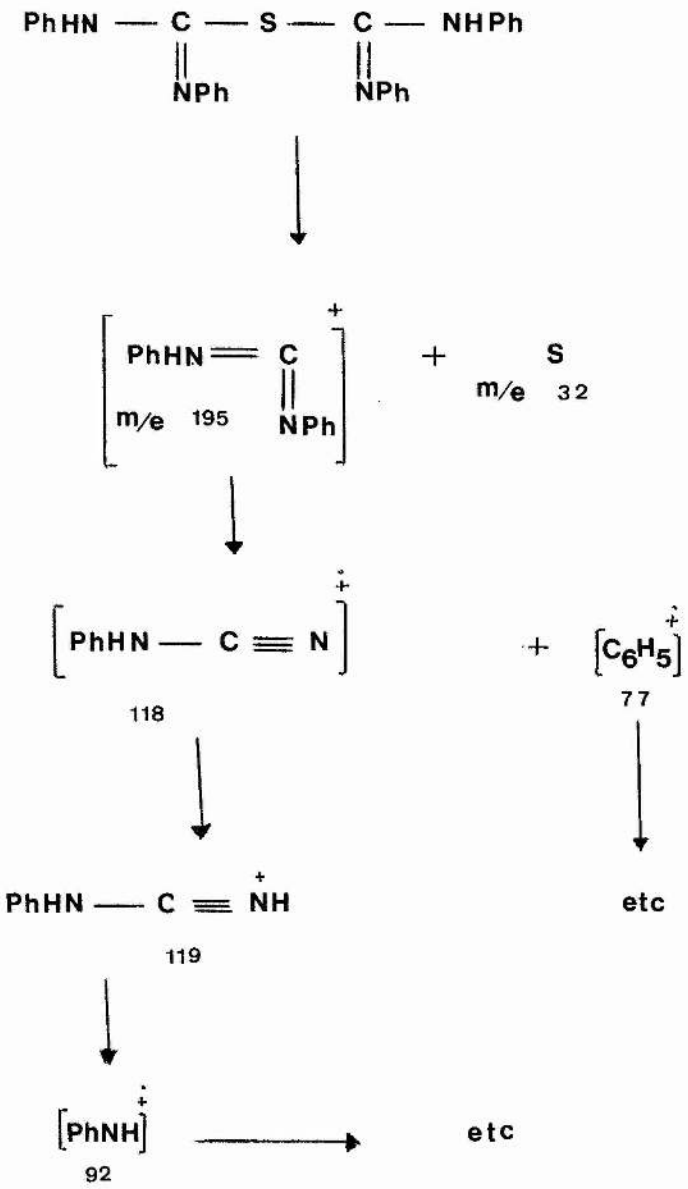
The first step is to examine systematically the products of oxidation of N-substituted thioureas under different experimental conditions.

1) 1-Phenylthiourea

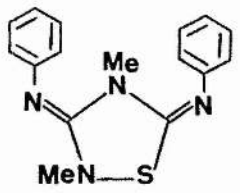
Reaction with a two-fold excess of any one of three oxidising agents, hydrogen peroxide, nitrous acid, and bromine in ethanol gave the same product, Hector's Base. The product was obtained in high yield and no isolable heterocyclic by-products were obtained. With dry chloroform as solvent the product on oxidation with bromine was 2-aminobenzothiazole (72). Addition of a small quantity of water resulted in a marked diminution in the yield of this material.

2) 1-Methyl-3-phenylthiourea

Reaction with any of the above oxidising agents in ethanol resulted in formation of the same compound (74). Nitrous acid was the oxidant used by Christophersen et al (1975) in preparing this material for their X-ray study and the products of the other reactions were shown to be identical by mixed melting point and by comparison of the nmr spectra.


PhHN — C — S — C — NHPh
NPh
NPh
PhHN = C
NPh
m/e 195
+
S
m/e 32
PhHN — C ≡ N
118
+
C6H5
77
PhHN — C ≡ NH
119
etc
PhNH
92
etc

SCHEME 15



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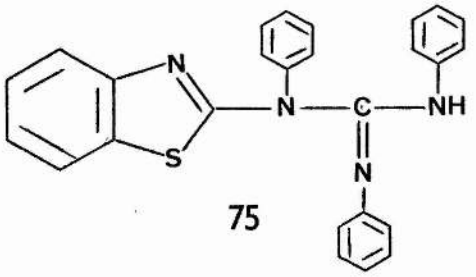

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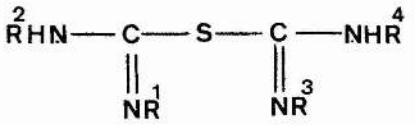

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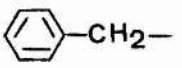
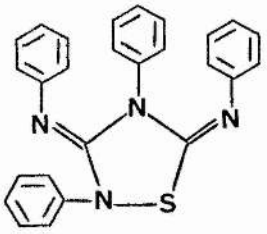
a $\overset{2}{R} = \overset{4}{R} = Ph \quad \overset{1}{R} = \overset{3}{R} = H$

b $\overset{2}{R} = \overset{4}{R} = Ph \quad \overset{1}{R} = \overset{3}{R} = Me$

c $\overset{1}{R} = \overset{2}{R} = \overset{3}{R} = \overset{4}{R} = Ph$

d $\overset{1}{R} = \overset{2}{R} = \overset{3}{R} = \overset{4}{R} =$ 



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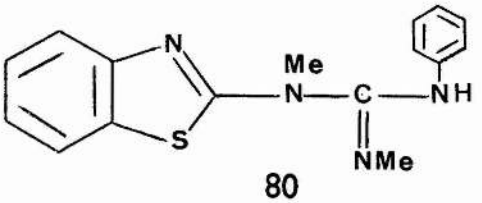

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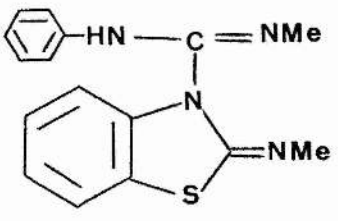

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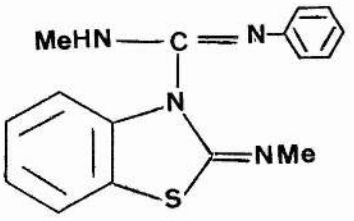


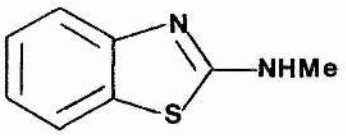
82

3) 1, 3-Diphenylthiourea

This material is only slightly soluble in ethanol. Therefore, it was dissolved in chloroform and ethanol was added until precipitation commenced. Then the oxidising agent was added. Two compounds (78c) and (75) were isolated from the product of reaction while the latter predominated. No compound equivalent to (74), ie (79), was obtained. The Hugerschoff Base (75) is the product of interest and we will consider its identification later. For the moment we will limit discussion to the other product of reaction (78c).

Elemental analysis of (78c) indicated an empirical formula of $C_{26}H_{22}N_4S$, but no molecular ion peak in the mass spectrum corresponding to this formula was observed. It probably fragmented into two halves (m/e 195) with elimination of elemental sulphur (m/e 32). The fragmentation pattern is shown in Scheme 15. There was a strong absorption in the ir spectrum at 1650 cm^{-1}, corresponding to the C=N group. In the proton nmr spectrum the aromatic protons formed an unresolved peak at δ 6.86-7.54 (20H) and there was a much smaller peak at 8.63 ppm, which we assigned to the two NH groups. The truly diagnostic feature of (78c) was its carbon-13 nmr spectrum. The presence of only five signals indicate a highly symmetrical molecule. If the mobility of the NH protons is considered then the reason for the symmetry is clear. The non-aromatic carbon atom resonates at δ 153.3 ppm and remains as a singlet in the off-resonance spectrum.

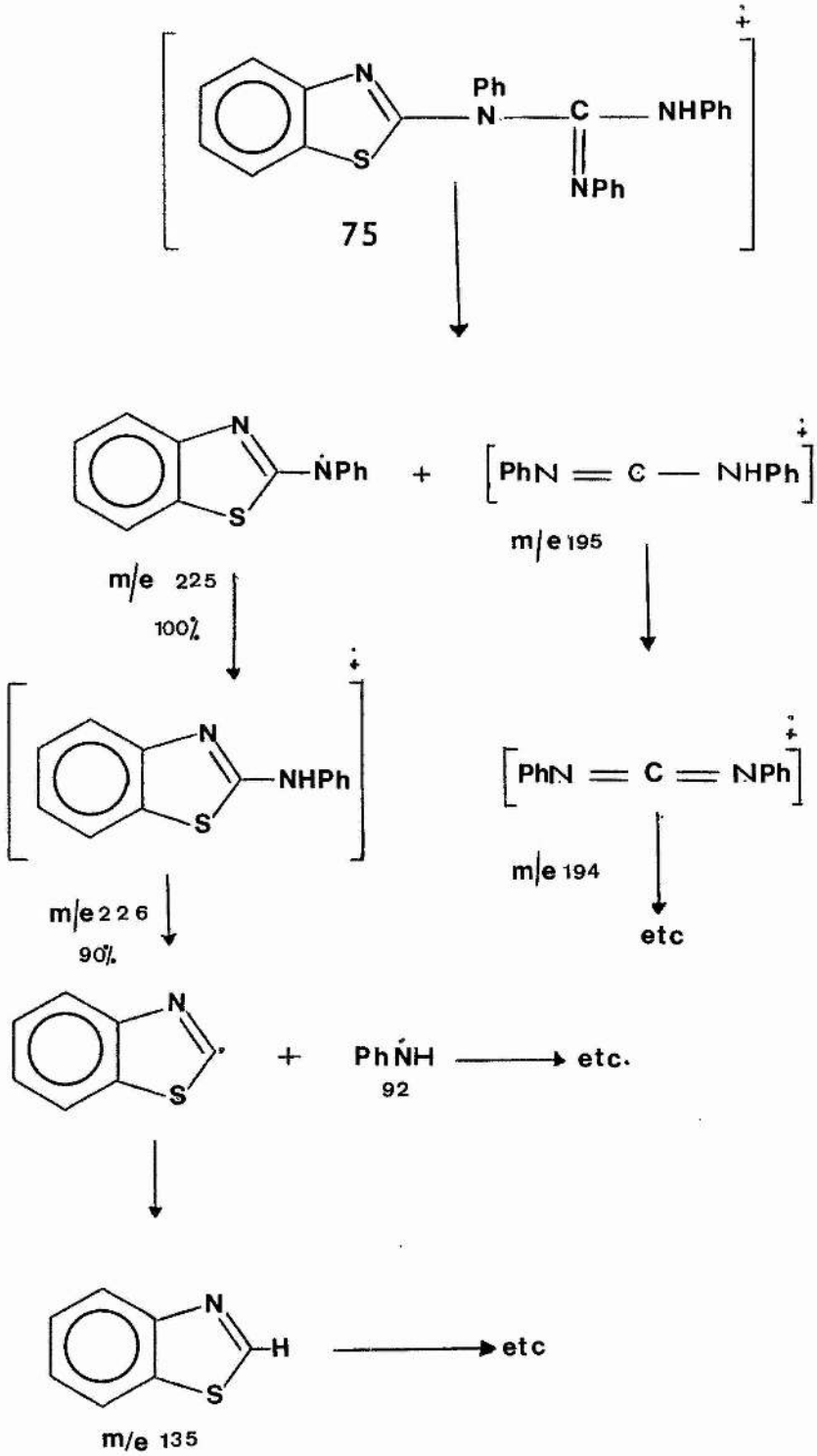
Before consideration of the mechanism of thiourea oxidation and the non-appearance of (80) as a reaction product, we must



83

discuss the structure of the Hugerschoff's Bases. From 1-methyl-3-phenylthiourea it is possible to prepare, in a manner which will be described presently, a Hugerschoff's Base for which at least three different structures (80)-(82) have been proposed (Verma and Sarkar, 1962; Suresh and Rao, 1960; and Srivastava, 1963).

Elemental analysis and the molecular ion peak in the mass spectrum indicate the correct molecular formula and from the ir spectrum it is clear that the molecule contains C=N and NH groups. From the proton nmr spectrum there is evidence for two different methyl groups, aromatic protons, and a single exchangeable proton at δ 4.95 (NH). The fact that the NH proton is not split means that (82) cannot be correct. In the carbon-13 nmr spectrum there were five signals for five non-protonated carbon atoms at δ 132.0, 146.9, 150.7, 151.2 and 164.7 ppm. In a model compound, 2-methylaminobenzothiazole (83), the chemical shifts of the non-protonated carbon atoms are at δ 117.7, 152.0 and 168.3 ppm (Christophersen et al, 1975). The correspondence between these and those of the Hugerschoff's Base are such that a structural assignment is not possible and the figures are consistent with both (80) and (81). The nitrogen-15 nmr spectrum of the Hugerschoff's Base has signals at δ -151, -191, -260, and -335 ppm (from nitromethane). In (81) there are almost two similar C=N groups but in the nmr spectrum all the signals are widely separated and so (80) is favoured. The last three signals are right for a guanidino system (see next chapter) which leaves the signal at δ -151 ppm assigned to the nitrogen of the thiazole ring. This value differs greatly from that reported (Witanowski, 1972) for


Ph
N
C
NHPh
NPh
75
m/e 225
100%
PhN = C — NHPh
m/e 195
NHPh
PhN = C = NPh
m/e 194
etc
m/e 226
90%
PhNH
92
etc.
etc
m/e 135

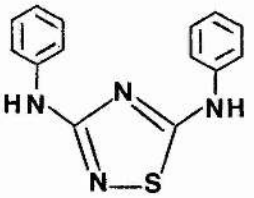
SCHEME 16

benzothiazole itself, where the signal is at δ -60 ppm. We cannot explain this discrepancy.

We can now consider the structure of the Hugerschoff's Base obtained from 1,3-diphenylthiourea, for which we have already proposed (75) by analogy with (80). There is no molecular ion peak in the mass spectrum but there are fragments (m/e 225, 195 and 135) which are consistent with the bond fissions as shown in Scheme 16. The mass spectra of compounds of this type have been considered by Joshua and Rajasekharam (1977) in some detail. The proton nmr spectrum showed only a number of overlapping aromatic protons and the NH protons could not be discerned. In the carbon-13 nmr spectrum there were signals corresponding to the protonated aromatic carbon atoms in the range δ 118.1-131.9 and seven other signals, which remained as singlets in the off-resonance spectrum at δ 132.46, 140.87, 143.07, 143.15, 145.67, 150.55 and 164.48 ppm. These data are consistent with structure (75). In the nitrogen-15 nmr spectrum there are only two signals. One at δ -120 ppm which we assign to the nitrogen of the benzothiazole ring and the other, at δ -260 ppm, to the NPh group. Because of the tautomerism of the two terminal NPh groups results in broadening and so signals for these two nitrogens are not observed (Levy and Lichter, 1979).

The key observations in proposing a mechanism which explains the different products obtained on oxidation of thioureas is the conversion of 3,5-bis(phenylimino)-1,2,4-thiadiazolidines like (74) into Hugerschoff's Bases. Joshua and Rajasekharam (1977) reported

76



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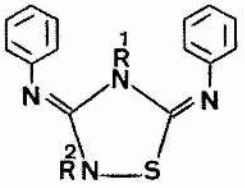
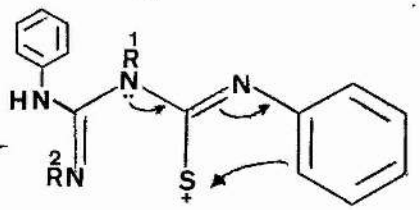


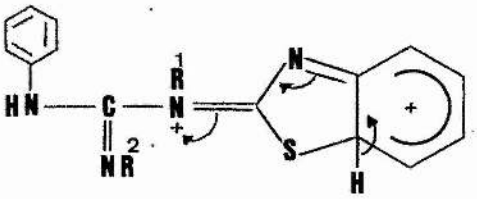
$R^1 = R^2 = Me$

74

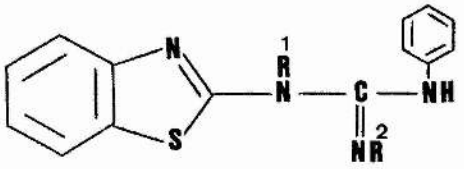


86

slow



87

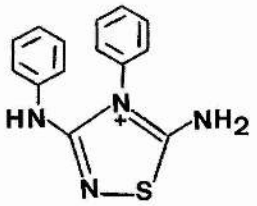


$R^1 = R^1 = Me$

80

$R^1 = R^1 = Ph$

75



88

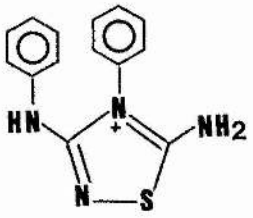
SCHEME 17

that, in the oxidation of 1-methyl-3-phenylthiourea, both (74) and (80) are formed, but that the relative amounts of (74) and (80) decreases if the acidic solution is allowed to stand. Christophersen et al (1975) refluxed (74) in a 1 M HCl for 45 minutes and obtained (80) in 82% yield. It seems possible that no (79) is isolated from the oxidation of 1,3-diphenylthiourea because it is susceptible to acid-catalysed rearrangement and rapidly converted into the Hugerschoff's Base (75). This was confirmed by experiment.

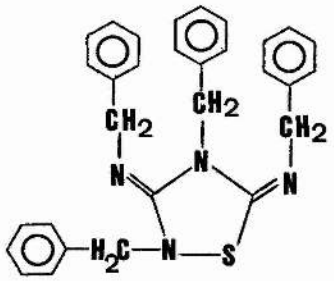
With the oxidising agents used so far, either acid is added or generated during the reaction. However, Kinoshita et al (1976) reported that 1,2,4-thiadiazolidines may be prepared from thioureas by oxidation with benzoyl peroxide (BPO). We are not concerned here with their proposed radical mechanism, but this synthetic procedure did permit isolation of a small quantity of (79). The main products of reaction were still (75) and (78c). The structure of this product (79) was deduced by Kinoshita et al (1976) from an examination of the mass spectrum. When (79) was warmed with 1 M HCl for a few minutes and the product extracted was found to be (75). We conclude, therefore, that Hugerschoff's Bases are formed from thioureas via 1,2,4-thiadiazolidines. The ease of acid-catalysed rearrangement depends dramatically upon the substitution. With four phenyl groups ie. (79) it is rapid but, if two are replaced by methyl groups, ie. (74), then reaction occurs much less readily. Hector's Base (76) and Dost's Base (77) may be recovered unchanged from boiling 1 M HCl. Methylation has no effect for (84) and (85) are equally unreactive.

We now suggest a mechanism of reaction which is consistent with these observations. As the rearrangement is acid-catalysed and involves cyclisation we propose electrophilic substitution by electrophilic sulphur (Scheme 17). The productive protonation of the 1,2,4-thiadiazolidine is at N(2) and fission of the N-S bond generates a sulphenium ion. Positive sulphur is a weak electrophile but the phenyl group under attack is activated, as shown in (86), by the amidino group. The slow step is electrophilic attack to give the intermediate (87), from which rapid irreversible proton loss occurs to give the product. If R=Me then N(2) will be strongly nucleophilic and recyclisation is the predominant reaction. The alternative path to (87) is, therefore, disfavoured. However, if R=Ph then N(2) is much less nucleophilic and formation of (87) a more likely process. We have, thus, explained the effect of substitutions upon the reaction rate.

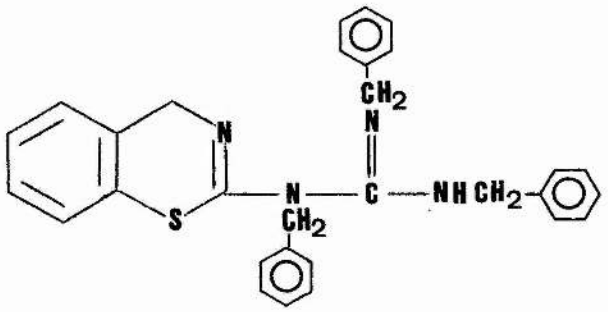
Hector's Base does not undergo a similar reaction for two reasons. Firstly, protonation of the exocyclic NH group produces a heteroaromatic cation (88) and thus protonation at N(2) is diminished. There is experimental evidence to support exocyclic protonation (Butler, 1978). Second, there is no appropriately placed phenyl group for cyclisation and fission of the N-S bond could only result in fragmentation of the molecule and loss of aromaticity. Dosts's Base (77) is already heteroaromatic and fission of the N-S bond is highly unlikely in view of the aromaticity lost, although there is a phenyl group right for attack by electrophilic sulphur. The aromaticity of Dost's Base is probably the driving force behind its formation (Dost, 1906) from



88



89



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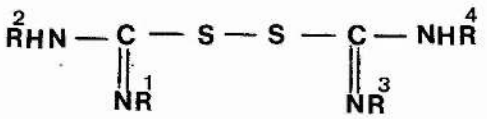


91

a. $R^2 = R^4 = Ph$, $R^1 = R^3 = H$

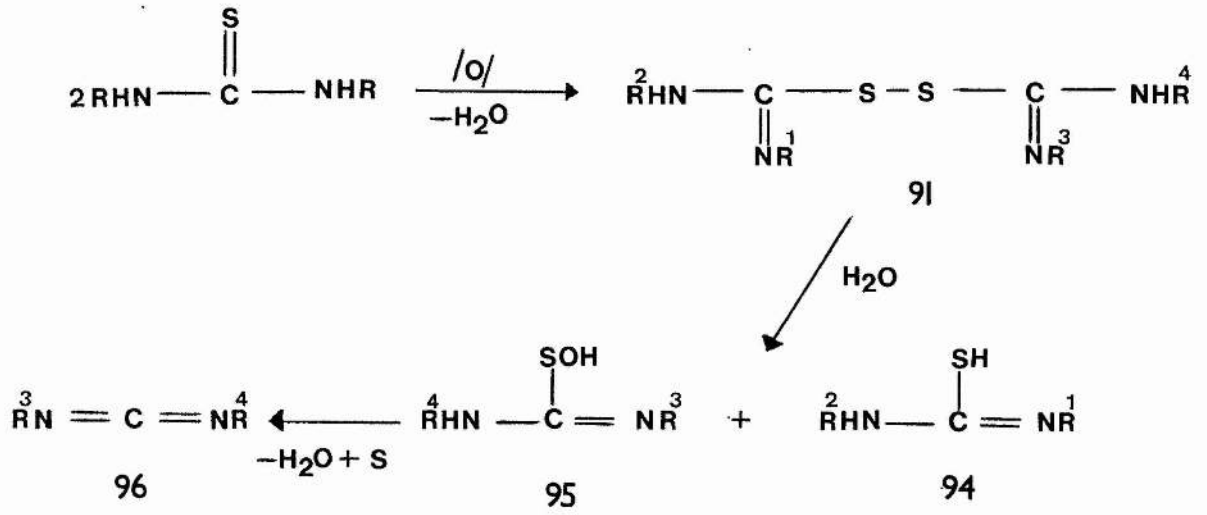
b. $R^1 = R^4 = Ph$, $R^2 = R^3 = Me$

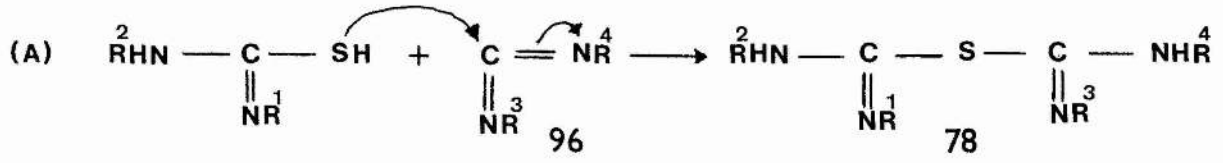
c. $R^1 = R^2 = R^3 = R^4 = Ph$

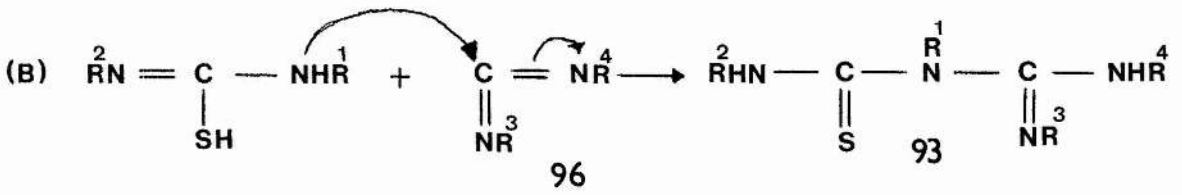
Hector's Base by heating the latter with ethanolic ammonia in a sealed tube.

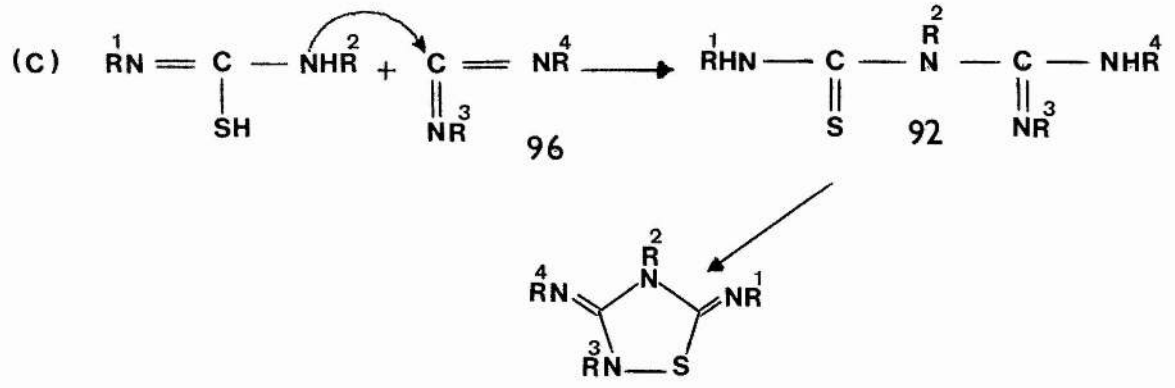
We can test the activating effect of the amidino group upon the phenyl group by examining the effect of the insertion of a methylene group between the two. 2,4-Dibenzyl-3,5-bis-(benzylimino)-1,2,4-thiadiazolidine (89) was prepared by oxidation of 1,3-dibenzylthiourea with BPO (Kinoshita et al 1976). Formation of (90) is possible if the sulphenium ion intermediate reacts in the same manner as previously described. However, the action of boiling 1 M HCl on (89) was the formation of 1,3-dibenzylurea as the only isolable product. Thus, it is clear that the activation of phenyl group is necessary if cyclisation is to occur.

The remaining problem is the formation of 1,2,4-thiadiazolidines resulting from oxidation of thioureas with various oxidising agent. In the past, several mechanistic schemes (Srivastava, 1963; Kurzer and Sanderson, 1959, 1963; Joshua and Rajasekharam, 1977; and Kinoshita et al, 1976) have been proposed, but none of them seems to be conclusive. In view of this complexity, we revised the oxidation of N-substituted thioureas (1-phenylthiourea, 1-methyl-3-phenylthiourea and 1,3-diphenylthiourea) with hydrogen peroxide, nitrous acid, BPO and bromine in acid solution. In each case identical compounds (76, 74 and 79) were obtained, no matter what the oxidant might be. Compound (79) was found to be extremely sensitive to acid and readily rearranged to (75). The cause of this rearrangement had already been explained. However, we









73 $R^1 = R^3 = H$, $R^2 = R^5 = Ph$

74 $R^1 = R^4 = Ph$, $R^2 = R^3 = Me$

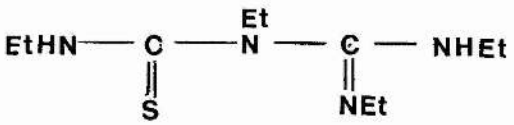
79 $R^1 = R^2 = R^3 = R^4 = Ph$

SCHEME 18

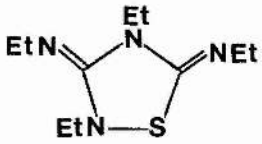
propose a reaction mechanism in Scheme 18, where rapid consumption of oxidant but slow appearance of sulphur suggests several steps. There appears to be a general agreement that the first step in the reaction is formation of a dithiobisformamidine, ie. (91) (Sahasrabudhey and Nambury, 1958; Kurzer and Sanderson, 1959, 1963; and Srivastava, 1963). This compound (91) was also prepared by partial oxidation of 1-phenylthiourea (Kurzer and Sanderson, 1959). It is insoluble in nonpolar solvents and in polar solvents it dissolves with slow formation of colloidal sulphur. Thus, no spectral data could be obtained with solvents regularly used for nmr spectroscopy. However, it is soluble in TFA without formation of sulphur and could be recovered unchanged from this solvent. Although, none of the spectral data recorded characterises the material yet, it is certainly not 1-phenylthiourea. Compound (91a) is a white solid, melts at 146° (lit. m.p. 96-100°, dec., Kurzer and Sanderson, 1969) and shows depression in mixed melting point (100-120°) with pure 1-phenylthiourea. The mass spectrum does not provide any useful information except peaks at m/e 79, 80, 81 and 82 which are due to Br^{79}, HBr^{79}, Br^{81} and HBr^{81}. The most striking feature in ir spectrum is that the stretching vibration of C=S is missing while in pure phenylthiourea it absorbs at 1060 cm^{-1}. The proton nmr spectrum exhibits a multiplet at δ 7.34-7.72 (10H) and a broad singlet at 8.06 (2H) ppm, while the remaining two NH protons exchange with solvent. The carbon-13 nmr spectrum is equally good and, shows three resonances at δ 127.22, 133.04 and 134.25 ppm while phenylthiourea have five absorption at δ 127.19, 131.61, 131.82, 134.92 and a broad one at 170.31 (C=S) ppm.

Moreover, compound (91a) does not show any absorption pertaining to C=S and, C=N peak probably, has supressed due to the effect of quadrupole moment of nitrogen atoms situated on either side of carbon. Despite this, heavy protonation on nitrogen atoms may have further aggravated the situation. In addition to these facts, we also feel that the evidence adduced by Kurzer and Sanderson (1959) is sufficiently convincing to make structure (91a) certain.

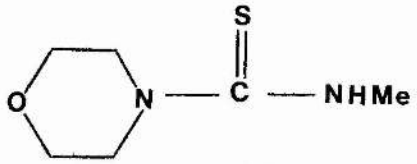
Srivastava (1963), Joshua and Rajasekharam (1977) have suggested that dithiobisformamidine (91c) ($R^1=R^2=R^3=R^4=Ph$) changes to monosulphide (78c) which in turn isomerises to (92) and (93), each leading to different thiadiazoles upon cyclisation. We were successful in isolating (78c) alongwith (75) and (79) in the oxidation of 1, 3-diphenylthiourea. The yield of (78c) depends upon the nature of oxidant as has been mentioned in Experimental section. When compound (78c) in our present oxidative conditions was stirred at room temperature and at boiling state, nothing new was obtained and starting material was recovered. However, our findings do not agree with the work of Srivastava (1963), Joshua and Rajasekharam (1977), but partially support the assignment of Kurzer and Sanderson (1959). The hydrolytic cleavage of disulphide link of (91) yields N-substituted thiourea (94) and an intermediate highly labile sulphenic acid (95). The existence of an analogous sulphinic acid $H_2N-\overset{NH}{\overset{\|}{C}}-SO_2H$ obtained from thiourea or dithioformamidine salts on oxidation is well established (Barnett, 1910; and Boesken, 1936, 1948). Decomposition of the hypothetical intermediate (95) might proceed to (96) which in turn condensed with N-substituted thiourea to yield (92) and (93), especially


EtHN
C
S
Et
N
C
NEt
NHEt

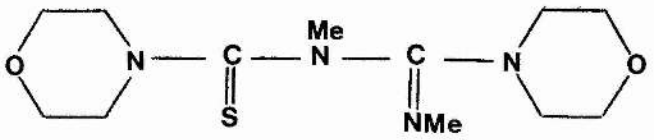
97


Et
N
EtN
NEt
EtN
S

98

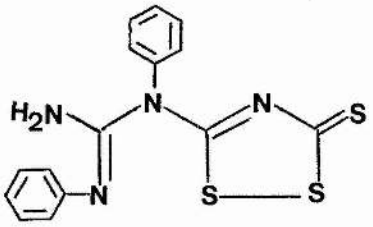

S
O
N
C
NHMe

99


O
N
C
S
Me
N
C
NMe
N
O

100

when N-substituents are different. If the N-substituents are similar then only one product will dominate. In the oxidation of 1-methyl-3-phenylthiourea with nitrous acid, the product isolated was conclusively shown to possess the structure (74) studied by X-ray crystallographic technique (Christophersen et al, 1975). Apparently then, during condensation the NR^2 (R^2=Me, R^1=Ph) group which is the more nucleophilic part of molecule will attack (96) first to give (92) and formation of (93) seems to be unlikely (Scheme 18). It is a well known fact (Joshua, 1962) that amidinothioureas which are the precursors of thiadiazoles can be obtained by the condensation of cyanamides or carbodiimides with the appropriate thioureas. Further evidence comes from the hydrogen sulphide reduction of (74) in acidic solution is (92), not (93) (Joshua, 1977). Hence we believe that intermediate (96) is essential and plays a very important role in the formation of amidinothioureas (92) which subsequently, under oxidative conditions change to 1,2,4-thiadiazoles. More recently, an intermediate (97) akin to (92) was isolated by Kinoshita et al (1976) on oxidation of 1,3-diethylthiourea with a limited amount of BPO. Its structure was confirmed by several means and further reaction with BPO gave 2,4-diethyl-3,5-bis-(ethylimino)-1,2,4-thiadiazolidine (98). Similarly, treatment of N-methyl-4-morpholinethiocarboxamide (99) with BPO gave N^1,N^2-dimethyl-N^1-morpholinothiocarbonyl-4-morpholine-carboxamidine (100) which is also an analogue of the intermediate (92) and provides unambiguous proof that it is the amidinothioureas which are the precursors of 1,2,4-thiadiazoles and monosulphide (78)



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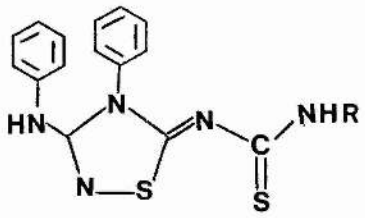
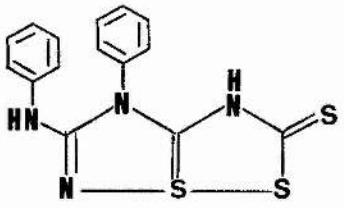


102

a, R = Ph

b, R = Me



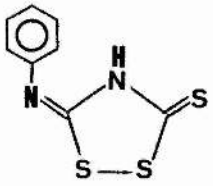
103

has nothing to do with it. Compound (78) came out during oxidation process as a side product (Scheme 18). The structure of (100) was determined by X-ray analysis (Kinohita et al, 1976).

Effect of base on Hector's Base adducts

Hector's Base (76) (Hector, 1889) forms adducts of two different types. With carbon disulphide the original ring opens and a new ring forms to give (101) (Fromm and Heyder, 1909) and Glidewell et al (1978) confirmed its structure by X-ray crystallographic method. But, with phenyl and methyl isothiocyanates, addition gives (102a) and (102b) as will be discussed in detail in the next chapter. The reaction stops at that stage and no new ring forms. It is probable that the first step in the formation of (101) is an adduct of type (102) and ring opening and cyclisation are subsequent steps, possibly going through an intermediate (103) containing 'hypervalent' sulphur. We thought it might be possible to make (102) continue the reaction sequence, with formation of a ring containing an S-S bond, by action of a base. We examined, therefore, the action of base on both (101) and (102).

Reaction of (101) with sodium hydroxide in methanol/DMF solution resulted in formation of yellow solid of formula $C_8H_6N_2S_3$. The ir spectrum suggested the presence of NH, C=N and C=S groups and from the carbon-13 nmr spectrum we deduced that there are three tertiary carbon atoms at δ 137.9, 179.1 and 209.3 ppm. These data are consistent with structures (104) and (105) but we prefer the latter, 5-anilino-3H-1,2,4-dithiazole-3-thione, as with all the compounds of this series we have examined the double



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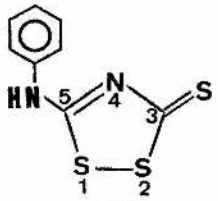

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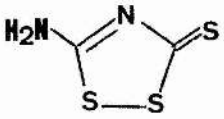

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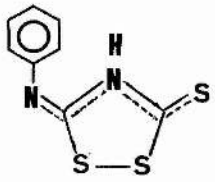

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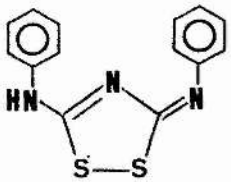

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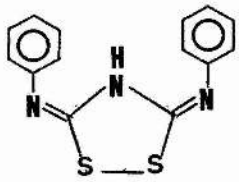

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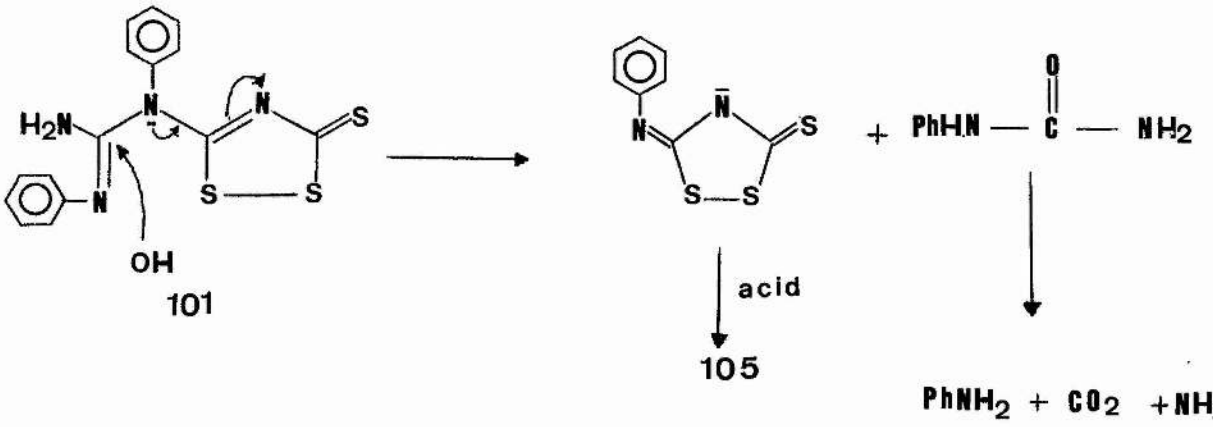


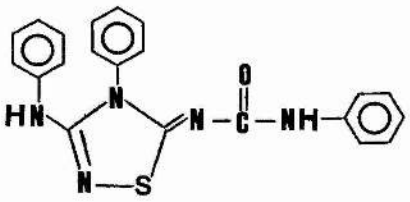
101

105

SCHEME 19

bond is in the ring whenever possible (see Chapter 5). Also, X-ray crystallographic studies have shown that xanthane hydride (106) made by the action of acid on ammonium thiocyanate (Cotton and McCleverty, 1967), is 5-amino-3H-1,2,4-dithiazole-3-thione (Hordvik, 1963), although 5-imino compound is possible. The fact is that nitrogen-15 nmr spectrum neither favoured (104) nor (105) but reflects the existence of (107) in solution which is the hybride structure of (104) and (105). There are two nitrogen atoms in (107) but only one appears in the spectrum at δ -114.7 ppm, which we assign to the nitrogen of the dithiazole ring. Because of rapid tautomerism between two structures (104) and (105) results in broadening of NPh signal, so the resonance for this nitrogen is not observed (Levy and Lichter, 1979). The proposed mechanism for the formation of (105) from (101) is shown in Scheme 19.

Reaction of (102) with base under the same reaction conditions gave a similar product, $C_{14}H_{11}N_3S$ for which we propose structure (108) by analogy with (105). The ir spectrum indicates the presence of NH and C=N groups. In the carbon-13 nmr spectrum there is only one non-aromatic tertiary carbon atom and this might suggest that the structure is (109). However, the shift of this tertiary carbon (δ 168.5 ppm) is inbetween that observed for a ring double bond (δ 176.3 ppm) and an exocyclic double bond (δ 153.5 ppm) in related compounds (see Chapter 5). This intermediate value would be expected for a tautomeric mixture of the two identical forms of (108) and (109). Further confirmation



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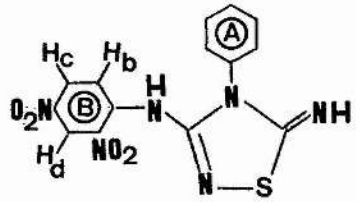

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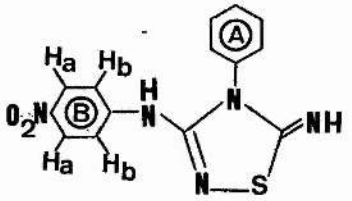

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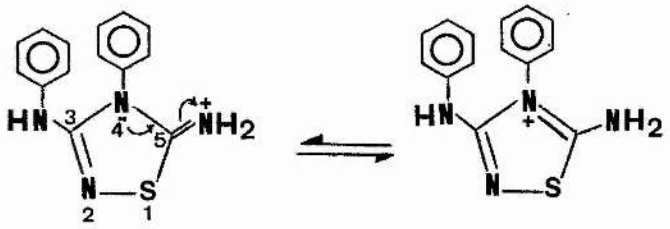
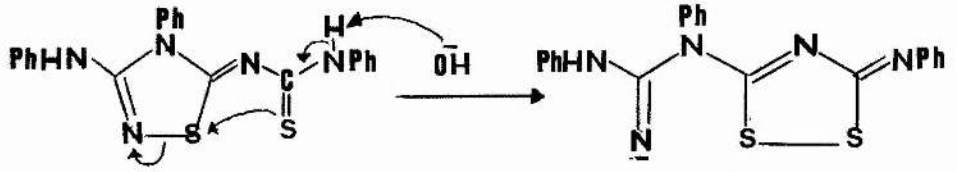


76 88



102a

as scheme 19

108

SCHEME 20

comes from nitrogen-15 nmr studies. Again there are two nitrogen atoms in (108) but only one appears at δ 155.0 ppm. The reason for the disappearance of second nitrogen (NPh) has already been explained. Hence, we believe that compound (108) in solution exists as (110). The proposed mechanism for the formation of (108) is shown in Scheme 20. We were, therefore, successful in forming a ring with an S-S bond from (102a).

Two other adducts of Hector's Base, with methyl isothiocyanate (102b) and phenyl isocyanate (111) were examined. The former reacted with sodium hydroxide with elimination of sulphur and from (111) the starting materials were recovered unchanged. These reactions were not examined further.

Nitration of Hector's Base

Nitration of Hector's Base (76) yields two compounds (112) and (113). Elemental analysis and molecular weight determination correspond to the mono (112) and dinitro (113) products of Hector's Base. The nmr spectra of these compounds reflect that only one out of two phenyl rings involves in the nitration process. The exocyclic nitrogen of Hector's Base seems to be more basic than others and carbon-13 nmr spectrum confirms this assignment. The chemical shift of C(5) in thiadiazole ring of Hector's Base in DMSO resonates at δ 164.6 while in TFA at 180.0 ppm. This downfield shift indicates that it is the exocyclic nitrogen of Hector's Base which is heavily protonated and casues dramatic deshielding effect on phenyl ring attached to next nitrogen at position 4 (88).

Butler (1978) also shared this view. Hence, the anilino part of the molecule is nitrated under our experimental conditions.

Hector's Base in a nitrating mixture (52% H_2SO_4 + 70% w/w HNO_3, 10:1) gave yellow coloration which absorbed at λ_{max} 347 nm in uv/visible region. The absorption went on increasing with the passage of time and became constant when all the substrate had been consumed. There was no movement of the isosbestic point. A similar kind of effect was observed at SP700 spectrophotometer. The nature of the curve indicated that probably there was mononitration. However, under identical experimental conditions, when Hector's Base was stirred in the same nitrating mixture on a preparative scale for ten minutes, a yellow solid was obtained. It had a molecular ion peak at m/e 313, suggesting a mononitrated product (112). In the proton nmr spectrum at 360 MHz, there were two doublets at δ 7.83 (2H, J_{ba} 9 Hz) and 8.21 ppm (2H, J_{ab} 9 Hz). The first doublet was assigned to H_b and the second one to H_a protons. The nature of coupling constant and the shape of splittings exhibited that in compound (112), the nitro group was at the para position of the ring. Two other singlets at δ 7.73 and 7.80 ppm were due to phenyl ring (A) protons and NH proton. The second NH proton, probably, exchanged with solvent.

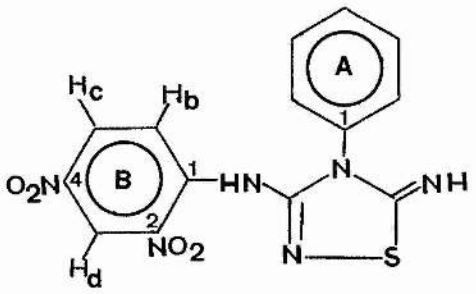
Further confirmation comes from carbon-13 nmr spectrum. There are five tertiary carbons in (112) which absorb at δ 132.06, 142.16, 145.10, 148.26 and 176.93 ppm, respectively. The first three shifts are ascribed to nonprotonated aromatic carbons while the last two belong to thiadiazolidine ring. All these carbons remain unsplit in the off-resonance spectrum and

112a

their chemical shifts are well in agreement with the literature values. The ir spectrum is consistent with NH, C=N and NO_2 groupings in (112).

The same compound (112) was obtained when Hector's Base in aqueous nitric acid (50 ml 70% w/w HNO_3 + 25 ml H_2O) was stirred for 3 h at room temperature. It melts at 170° and then explodes. The cause of explosion is probably due to the presence of very small amount of nitroso compound as impurity in (112), otherwise the spectral data are identical. In uv/visible region it absorbs at λ_{max} 352 and 232 nm (ϵ = 11554 and 13904) and in the nitrating mixture (52% H_2SO_4 + 70% w/w HNO_3, 10:1) at 347 nm while the absorption at 232 nm which we attribute to phenyl ring (A) completely disappeared. The cause of the disappearance is probably associated with protonation of exocyclic nitrogen resulting in creation of positive charge on nitrogen (112a). A small hypsochromic shift ie. from 352 to 347 nm is due to solvent used. Similarly, Hector's Base in the same nitrating mixture shows an identical absorption pattern and thus confirms the formation of p-nitro product (112). Besides this, we have found that compound (112) in the same nitrating mixture from which it has been recovered, does not go to further nitration. As the second nitration step is slow and shape of curves should have been different if the second nitration had occurred. But the fact is that no alternation in uv/visible spectra at SP800 and SP700 spectrophotometer has been seen.

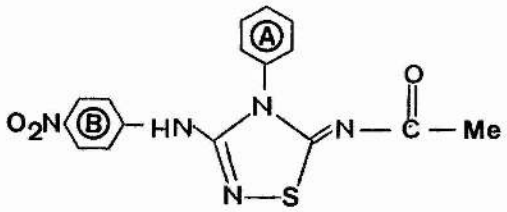
In a comparatively stronger nitrating mixture (conc. H_2SO_4 + conc. HNO_3, 2:1), Hector's Base yields only a single product, ie. dinitrated compound (113). Again two nitro groups are on the same



113

phenyl ring, suggesting that other phenyl ring (A) is not involved in the nitration process whatever the concentration of nitronium may be. Elemental analysis and molecular ion peak at m/e 358 are consistent with molecular formula of $C_{14}H_{10}N_6O_4S$. It melts sharply at 158° and the application of HPLC technique as described in experimental section confirms its purity. The proton nmr spectrum at 100 MHz in ($^2[H_6]$DMSO) exhibits two doublets (δ 8.63 and 8.83 ppm), a singlet (8.7 ppm) and another singlet at δ 7.8 ppm which is assigned to phenyl ring (A) protons. The first doublet at δ 8.63 (1H, J_{bc} 2 Hz) and the second one at 8.83 (1H, J_{cb} 2 Hz) are ascribed to protons H_b and H_c. The singlet at δ 8.7 ppm is assigned to H_d proton. Proton H_d in this spectrum does not appear to couple with proton H_c, but at 360 MHz in ($[^2H_6]$acetone) it couples with H_c and gives rise to a doublet centred at δ 9.0 ppm (1H, J_{dc} 2H). In turn, H_c couples both with H_d and H_b to yield two doublets centred at δ 8.68 ppm (1H, $J_{cb,cd}$ 2 Hz) which are almost overlapping. The phenyl ring (A) protons resonate at δ 7.93-8.0, and 7.85-7.88 ppm (total 5H), and two NH protons at 9.08 and 9.11 ppm, respectively.

In the carbon-13 nmr spectrum, a collection of protonated aromatic carbons appears at δ 120.6-132.4 and other non-protonated carbons at 135.44 (C_2), 138.11 (C_4) and 140.68 (C_1) ppm. Two more resonances of thiadiazolidine ring carbons exist at δ 146.67 and 176.23 ppm. The chemical shift of C_1 of phenyl ring (B) coincides with the chemical shift of nonprotonated carbon of phenyl ring (A). This is because of shielding effect of



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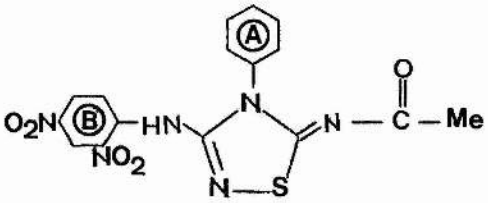

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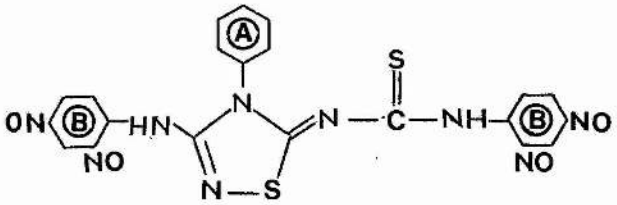
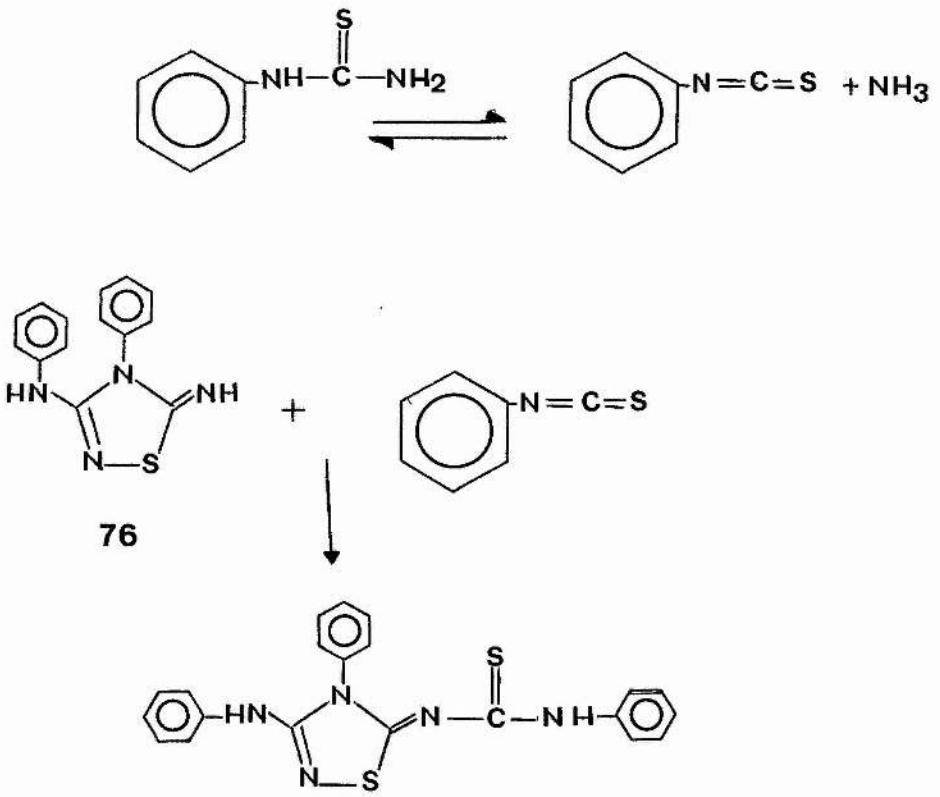


116

nitro group to adjacent carbons (Levy and Nelson, 1972).

Further support for (112) and (113) arises from nitration of Hector's Base in glacial acetic acid. Two products (114) and (115) were isolated with acetyl group at exocyclic nitrogen. Compound (114) melts at 204° and has only one nitro groups at para position of phenyl ring (B). Elemental analysis, molecular ion peak, nuclear magnetic resonance and infrared spectal data are consistent with structure (114). Similarly, compound (115, m.p. 310°) contains two nitro groups at ortho and para positions of anilinophenyl ring and its structure is concordant with spectral data (see Experimental section). Moreover, acetylation of compounds (112) and (113) yield compounds (114) and (115) which is a direct proof for the identity of formers.

As has been mentioned previously that the oxidation of 1-phenylthiourea with a limited amount of nitrous acid affords Hector's Base. We thought it would be of great interest if we could nitrate Hector's Base (as aerial oxidation of nitroso to nitro compound in aqueous media is well known) by increasing the amount of nitrous acid in the reaction mixture. Two products (102a) and (116) were isolated. Compound (102a) melted at 220° and was identified by comparison with authentic sample. The spectral data are given in Experimental section. The second product (116) exploded at 189° and solubility problem in all regular solvents used for nmr spectroscopy precluded confirmation of its structure. However, we managed to dissolve a small quantity of it in DMSO-d_6. The proton nmr spectrum consisted of



SCHEME 21

one multiplet (δ 7.07-7.55 ppm) and two singlets at δ 7.72 and 8.9 ppm with an integration ratio of 6:5:1, which suggested that both anilino rings (B) had been nitrosated resulting in (116). But, it is not clear yet, whether compound (116) contains nitro or nitroso groups or the mixture of both. Because of the highly explosive nature of (116) we think that elemental analysis and mass spectrum cannot help in the confirmation of its structure. The ir spectrum is consistent with NH, C=N and C=S groups. In the carbon-13 nmr spectrum, carbons bearing nitroso/nitro groups do not appear because of longer spin-lattice relaxation time induced by quadrupole moment of the nitrogen. Other chemical shifts are in agreement with the features of (116). Hence, on the basis of facts and figures so far obtained, we tentatively favour this structure (116).

Despite this, we found that compound (102a) was on the way to (116). When excess nitrous acid (20 g $NaNO_2$) was used in the oxidation of 1-phenylthiourea, we did not find any trace of (102a) and the only product that we obtained was (116) (95% yield). The formation of (102a) is not surprising and even not unlikely. We believe that 1-phenylthiourea, in our experimental conditions, gets hydrolysed into phenyl isothiocyanate in addition to the formation of Hector's Base. The latter condenses with the former to give (102a) (Scheme 21). The same compound (102a) is obtained when pure samples of Hector's Base (76) and phenyl isothiocyanate are allowed to react in acetone.

EXPERIMENTAL

Hector's Base (3-anilino-5-imino-4-phenyl-Δ^2-1,2,4-thiadiazoline (76)

a) Phenylthiourea (5 g) was dissolved in a mixture of ethanol-water (1:1) and a few drops of conc. HCl added. Hydrogen peroxide (50 ml, 10% vol.) was poured into the solution with constant stirring at room temperature. After a few seconds, sulphur started separating. After one hour stirring, the sulphur was filtered off and the filtrate basified to give a white solid. It was recrystallised from an ethanol-acetone mixture. When dried, it had m.p. 183° (lit. m.p. 183°, Hector, 1889).

b) When the above experiment was repeated using sodium nitrite (4 g in 20 ml H_2O and 5 ml conc. HCl) and phenylthiourea (7.6 g) the same compound (76) was obtained, mixed m.p. 183°. Yield 70%.

c) When phenylthiourea (5 g) was oxidised with bromine (3 ml) in a similar way, a white solid was obtained. It was thoroughly washed with ethyl acetate and recrystallised from acetone, mixed m.p. 183°. Yield 60% (76)

2,4-Dimethyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine (74)

d) Compound (74) was obtained by oxidation of 1-methyl-3-phenylthiourea with hydrogen peroxide (80% yield), nitrous acid (65% yield) and bromine (60% yield) using the same conditions as mentioned above.

M.p. 130° (lit. m.p. 124°, Christophersen, 1975), m/e 296 (M^+), ν_{max} 1630 (C=N) and 1585 cm^{-1} (C=C), $\delta H(CDCl_3)$ 2.6 (3H, s), 3.4 (3H, s) and 6.9-7.3 (10H, m) ppm; $\delta C(CDCl_3)$ 31.75 (q), 40.0 (q), 119.5-130.60 (m), 147.50 (s), 149.1 (s), 149.5 (s) and 153.6 (s) ppm.

e) Compound (74) (0.01 mole) and hydrochloric acid (50 ml, 1 M) was refluxed for 45 minutes. On neutralisation with sodium hydroxide at 0°C, a white solid was thrown out and after recrystallisation from ethanol gave N-2-benzothiazolyl-N,N'-dimethyl-N''-phenylguanidine (80).

M.p. 119° (lit. m.p. 119°, Christophersen et al 1975), m/e 296 (M^+), ν_{max} 3260-3160 (NH), 1630 (C=N) and 1585 cm^{-1} (C=C) $\delta H(CDCl_3)$ 2.85 (3H, s), 3.4 (3H, s), 4.95 (1H, s) and 6.88-7.74 (9H, m) ppm. The peak at δ 4.95 ppm disappeared with addition of a few drops of D_2O, $\delta C(CDCl_3)$ 30.85 (q), 37.70 (q), 120.25-124.85 (m), 132.0 (s), 146.95 (s), 150.75 (s), 151.25 (s) and 164.75 (s) ppm. (Found: C, 65.02; H, 5.48; N, 18.8 $C_{16}H_{16}N_4S$ requires C, 64.84; H, 5.44; N, 18.78%)

f) 1,3-Diphenylthiourea (11.4 g) was dissolved in a minimum quantity of chloroform and diluted with its double volume of ethanol and water (100 ml). A few drops of conc. HCl were added and then hydrogen peroxide (60 ml of 20% vol.) dropwise with constant stirring. Sulphur separated immediately, it was removed, the organic solvents stripped off and the residue diluted with water and then basified with sodium hydroxide. A white solid was obtained which was recrystallised from ethyl acetate to give 2-(1,2,3-triphenylguanidino)benzothiazole (75).

M.p. 140° (lit. m.p. 136°, Hugerschoff, 1903), m/e 226 ($C_{13}H_{10}N_2S$) and 194 (PhN=C=NPh), ν_{max} 3260-3220 (NH) and 1655 cm^{-1} (C=N), $\delta H(CDCl_3$ 6.8-7.68 (aromatic protons), NH proton has mixed with aromatic ones, $\delta C(CDCl_3)$ 118.1-131.9 (protonated aromatic carbons, m), 132.46 (s), 140.87 (s), 143.07 (s), 143.15 (s), 145.67 (s), 150.55 (s) and 164.48 (s) (Found: C, 73.98; H, 4.66; N, 13.23 $C_{26}H_{20}N_4S$ requires C, 74.26; H, 4.79; N, 13.32%) Yield 60%.

The ethyl acetate insoluble material after multiple recrystallisation from a mixture of methanol and acetone (1:1) gave 1,2,3,4-tetraphenyl-α,α'-thiobisformamidine (78c)

M.p. 244°, m/e 195 (PhHN-$\overset{+}{C}$=NPh) and 32 (S), ν_{max} 3340-3280 and 3190 (NH), 1650 (C=N) and 1550 cm^{-1} (C=C), $\delta H([^2H_6]DMSO)$ 6.86-7.54 (20H, m) and 8.63 (2H, s) ppm, $\delta C([^2H_6]DMSO)$ 118.33 (d), 121.88 (d), 128.78 (d), 139.76 (s) and 152.61 (s) ppm (Found: C, 73.78; H, 5.43; N, 13.03 $C_{26}H_{22}N_4S$ requires C; 73.90; H, 5.24; N, 13.25%) Yield 20%.

g) Compounds (75) (yield 50%) and (78c) (yield 40%) were obtained when 1,3-diphenylthiourea was oxidised by sodium nitrite (4 g in 20 ml water and 5 ml conc. HCl) using same conditions as described above.

h) The above experiment (f) was repeated using liquid bromine (3 ml). The yield of compound (75) was 50% and (78c) 15%. There was no depression in their mixed melting points.

i) 2,4-Diphenyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine (79)

It was obtained by oxidation of 1,3-diphenylthiourea with benzoyl peroxide (Kinoshita et al, 1976) alongwith (75) (yield 40%) and (78c) (yield 40%).

j) 2,4-Dibenzyl-3,5-bis(benzylimino)-1,2,4-thiadiazolidine (89)

Oxidation of 1,3-dibenzylthiourea with BPO (Kinoshita et al, 1976) gave (89) (yield 70%) and 1,2,3,4-tetrabenzyl-α,α'-thiobisformamidine (78d), which had m.p. 204°.

M.p. 77° (lit. m.p. 81°, Kinoshita et al (1976), ν_{max} 1630 cm^{-1} (C=N), $\delta H(CDCl_3)$ 4.26 (2H, s), 4.34 (2H, s), 4.75 (2H, s), 5.06 (2H, s), and 7.18-7.23 (20H, m) ppm, $\delta C(CDCl_3)$ 47.50, 51.69, 56.61, 60.28, 126.39-128.60 (aromatic protonated carbons), 135.34, 137.38, 139.64, 141.20, 151.98 and 152.91 ppm.

M.p. 204°, m/e 223 ($PhCH_2NH\text{-}\overset{+}{C}\text{=}N\text{-}CH_2Ph$) and 32 (S) ν_{max} 3170 (NH) and 1610 cm^{-1} (C=N), $\delta H([^2H_6]DMSO)$ 4.53 (8H, s), 7.0-7.22 (20H, m) and 8.6 (2H, s) ppm.

k) Compound (79) (0.5 g) in HCl (50 ml, 1 M) was slightly warmed for a few minutes. The product was worked up as described in experiment (e), which gave (75), m.p. 140° and there was no depression in mixed melting point.

l) Compound (89) (2 g) in HCl (50 ml, 1 M) was refluxed for 2 h. On cooling a semi-solid mass appeared. It was washed with water and recrystallised from a mixture of methanol-acetone (2:1) which gave only dibenzylurea.

M.p. 168°, m/e 240 (M^+), ν_{max} 3320 (NH) and 1620 cm^{-1}

(C=O), δH([$^2H_6$]DMSO) 4.24 (4H, s), 6.46 (2H, s) and 7.22 (10H, s) ppm, δC([$^2H_6$]DMSO) 42.96, 126.41, 126.89, 128.07, 140.76 and 158.09 ppm

m) Compound (78c) (2 g) was dissolved in ethanol containing a few drops of conc. HCl. Hydrogen peroxide (20 to 40 ml) was added dropwise with constant stirring for 2 h at room temperature. No separation of sulphur occurred. On neutralisation with sodium hydroxide a white solid was obtained. It was recrystallised from methanol which gave the starting material (78c) confirmed by melting point and mixed melting point.

n) An ethanolic solution of (78c) (2 g) containing conc. HCl (2 ml) was refluxed for 2 h. After cooling, the product was worked up as described above. No change in the starting material was observed, m.p and mixed m.p. were 244°.

p) When experiment (m) was repeated with excess hydrogen peroxide but without acid, nothing new was obtained except starting material (78c).

q) Hector's Base (76) (2 g) in 5M HCl was refluxed for 1 h. After cooling, neutralisation and recrystallisation from methanol-acetone mixture, the starting material was obtained. No rearrangement occurred.

r) Similarly, no rearranged product, except starting material, was obtained when above experiment (q) was repeated with dimethylated Hector's Base (84) and Dost's Base (77).

s) Diaryl dithioformamidine (91a)

A suspension of finely ground 1-phenylthiourea (6.08 g) in chloroform (100 ml), to which water (6 ml) was added, was treated with bromine (20 ml, 0.02 mole) with stirring and external cooling (ice-water) during 8-10 minutes. The product was filtered off, washed successively with excess chloroform and light petroleum, ground in a mortar with more chloroform several times, collected and dried at room temperature.

M.p. 146° (lit. m.p. 96-100°, dec., Kurzer and Sanderson, 1959), mixed m.p. with pure 1-phenylthiourea 100-120°, ir spectra of (91a) and pure 1-phenylthiourea are non-identical, no molecular ion peak except at m/e 79 (Br^{79}), 80 (HBr^{79}), 81 (Br^{81}) and 82 (HBr^{81}), δH(TFA) 7.34-7.72 (10H, m) and 8.06 (2H, s) two NH protons have exchanged with solvent, δC(TFA) 127.22, 133.04 and 134.25 ppm δC(TFA) of PhNH-$\overset{S}{\overset{\|}{C}}$-$NH_2$, 127.19, 131.61, 131.82, 134.92 and 170.31 (C=S, broad) ppm.

t)1 The preparation of the adducts of Hector's Base has been described in Chapter 5.

The CS_2 adduct (101) (2.4 g) was refluxed with sodium hydroxide (3 g) in a mixture of methanol (60 ml) and DMF (30 ml) for 2 h. The reaction mixture went through a series of colour changes and ammonia was evolved. The cooled solution was poured into cold water and acidified. The yellow solid obtained 5-anilino-3H-1,2,4-dithiazole-3-one, was recrystallised from acetone (yield 80%), m.p. 160°, m/e 226 (M^+), ν_{max} (mull) 3185-3150 (NH), 1605 (C=N), 1560 (C=C) and 1017 cm^{-1} (C=S),

$\delta H(\text{[}^2H_6\text{]DMSO})$ 7.62-7.20 ppm (aromatic protons), $\delta C(\text{[}^2H_6\text{]DMSO})$ 121.5, 126.3, 129.4, 137.4, 179.1 and 209.3 ppm (Found: C, 42.56; H, 2.31; N, 12.44; S, 42.62 $C_8H_6N_2S_3$ requires C, 42.45; H, 2.67; N, 12.37; S, 42.42%), $\delta N(\text{[}^2H_6\text{]DMSO})$ -114.7 ppm (ext. ref. $CH_3{}^{15}NO_2$).

t)2 Treatment of (102a) in like manner gave 5-anilino-3-phenyl-imino-3H-1,2,4-dithiazole-3-thione (108) (yield 52%), m.p. 184°, m/e 251 (M^+-H_2S), ν_{max} (mull), 3170 (NH), 1620 (C=N) and 1585 cm^{-1} (aromatic C=C), $\delta H(\text{[}^2H_6\text{]DMSO})$ 7.06-7.40 ppm (aromatic protons), $\delta C(\text{[}^2H_6\text{]DMSO})$ 120.9, 123.9, 129.1, 146.4 and 168.5 ppm $\delta N(\text{[}^2H_6\text{]DMSO})$-155.0 ppm (ext. ref. $CH_3{}^{15}NO_2$) (Found: C, 58.57; H, 3.47; N, 14.95 $C_{14}H_{11}N_3S_2$ requires C, 58.92; H, 3.88; N, 14.72%)

u)1 Hector's Base (3 g) in a nitrating mixture (55 ml) (52% H_2SO_4 + 70% w/w HNO_3, 10:1) was stirred at room temperature for ten minutes and then poured into cold water with vigorous shaking. After neutralisation with sodium hydroxide a yellow solid settled out, washed thoroughly with water and then recrystallised from acetone which gave mononitro product of Hector's Base (112)

M.p. 208°, m/e 313 (M^+) ν_{max} 3290 (NH), 1630 (C=N), 1550 and 1335 cm^{-1} (NO_2), $\delta H(\text{[}^2H_6\text{]DMSO})$ at 360 MHz, 7.73 (5H, s), 7.80 (1H, s), 7.83 ($2H_b$, d, J_{ba} 9 Hz) and 8.21 ($2H_a$, d, J_{ab} 9 Hz), one NH proton has exchanged with solvent, $\delta C(\text{[}^2H_6\text{]DMSO})$ 119.39, 124.72, 128.88, 130.27, 131.12, 132.06 (s), 142.16 (s), 145.10 (s), 148.26 (s) and 176.93 (s). (Found: C, 53.99; H, 3.66; N, 22.16 $C_{14}H_{11}N_5SO_2$ requires C, 53.66; H, 3.53;

N, 22.35%) $\lambda_{max}^{CH_3CN}$ 352, and 232 (ε = 11554 and 13904), λ_{max} 347 in a nitrating mixture (52% H_2SO_4 + 70% w/w HNO_3, 10:1) Hector's Base (0.5 g/160 ml CH_3CN) (0.1 ml) in the same nitrating mixture gave λ_{max} 347 nm and absorption increased with time.

u)2 The same compound (112) was obtained when Hector's Base (2 g) in aqueous nitric acid (50 ml HNO_3 + 25 ml H_2O) was stirred for 3 h at room temperature. A yellow solid was collected, washed with water and recrystallised from acetone, m.p. 170° (explode) other data are the same as mentioned above.

u)3 Hector's Base (1 g) added bit by bit to a nitrating mixture (conc. H_2SO_4 + conc. HNO_3, 2:1 v/v) with constant stirring in an ice-bath for 1 h and then poured into cold water with vigorous shaking, collected yellow precipitate, washed with ice-water and recrystallised from hot water which gave bright yellow crystals of dinitro product of Hector's Base (113).

M.p. 158°, m/e 358 (M^+), ν_{max} 3340-3180 (NH), 1590 (C=N), 1510 and 1345 cm^{-1} (NO_2), δH($[^2H_6]$DMSO) at 100 MHz, 7.8 (5H, s), 8.63 ($1H_b$, d, J_{bc} 2 Hz), 8.83 ($1H_c$, d, J_{cb} 2 Hz) and 8.7 ($1H_d$, s) ppm δH($[^2H_6]$acetone) 7.85-7.88 and 7.93-8.0 (5H, m), 8.65 ($1H_b$, d, J_{bc} 2 Hz), 8.68 ($1H_c$, dd, J_{cb}, J_{cd} 2 Hz), 9.0 ($1H_d$, d, J_{dc} 2 Hz), 9.08 (1H, s) and 9.11 (1H, broad s) ppm, δC($[^2H_6]$DMSO) 120.61-132.43 (protonated aromatic carbons, m), 135.44 (s), 138.11 (s), 140.68 (s), 146.67 (s) and 176.23 (s) ppm, $\lambda_{max}^{CH_3CN}$ 323 and 212 nm, and in a nitrating mixture (52% H_2SO_4 + 70% w/w HNO_3, 10:1) 337 nm HPLC: column reverse phase, length 25 cm, injection 1γ mole of compd (113) in dioxane, wavelength 325 nm, detector uv, sensitivity

0.04 AU, pressure 95 bar, flow rate 2 ml/minute, chart speed 60 cm/1 h. (Found: C, 46.89; H, 2.79; N, 23.19 $C_{14}H_{10}N_6O_4S$ requires C, 46.92; H, 2.81; N, 23.45%)

v) Hector's Base (2.68 g) in a mixture of acetic acid (gl) and acetic anhydride (1:1) containing HNO_3 (1 ml of 70% w/w) was stirred for more than 5 h. After that reaction mixture was poured into cold water with shaking, collected a yellow solid, washed with water and ether. Recrystallised several times from acetone which gave very shining fluffy crystals of (114).

M.p. 204°, m/e 355 (M^+), ν_{max} 3230 (NH), 1610 (C=O), 1590 (C=N) 1545 and 1280 cm^{-1} (NO_2), δH($^2H_6$]DMSO) 2.15 (3H, s), 7.72 (5H, s), 8.2 ($2H_a$, d, J_{ab} 9 Hz), 8.75 ($2H_b$, d, J_{ba} 9 Hz) and 9.92 (1H) ppm, δC($^2H_6$]DMSO) 25.67, 120.02, 122.38, 125.78, 128.41, 130.37, 130.69, 133.34, 136.21, 145.62, 182.01 and 182.75 ppm (Found: C, 54.23; H, 3.81; N, 19.97 $C_{16}H_{13}N_5O_3S$ requires C, 54.07; H, 3.68; N, 19.70%)

The acetone insoluble material after several washings with DMSO gave (115), m.p. 310°, m/e 400 (M^+), ν_{max} 3200-3180 (NH), 1610 (C=O), 1580 (C=N), 1550 and 1330 cm^{-1} (NO_2), δC($^2H_6$]DMSO) 25.69 (-CH_3), 182.1 ($\overset{*}{C}$=N-C=O) and 182.78 (C=O) ppm, other shifts are very near to (113) (Found: C, 48.22; H, 3.02; N, 21.08 $C_{16}H_{12}N_6O_5S$ requires C, 47.99; H, 3.02; N, 20.99%)

w)1 Compound (112) (2 g) in a mixture of acetic acid (gl) and acetic anhydride (1:1) was stirred for 24 h. On dilution with water a yellow solid settled out, washed with water, ether and recrystallised from acetone which gave (114), m.p. and mixed

m.p., 204°.

w)2 Compound (113) (2 g) was acetylated as described. A yellow solid obtained and after several washings with DMSO gave (115), m.p. and mixed m.p. 310°.

w)3 Uv/visible spectra of compounds (112), (113) and Hector's Base (76) in acetonitrile solvent, and in nitrating mixtures were recorded on SP800 and SP700 spectrophotometers.

x) To aqueous ethanolic solution of 1-phenylthiourea (7.6 g) containing conc. HCl (5 ml) was added sodium nitrite (6.9 g in 30 ml H_2O) dropwise with constant stirring at room temperature for 1 h. A yellow solid settled out, washed with water, carbon disulphide, ether and recrystallised from hot acetone, which gave (116).

M.p. 189° (explode), ν_{max} 3300 (NH), 1610 and 1600 (C=N) 1550 and 1500 (NO or NO_2) and 1050 cm^{-1} (C=S), $\delta H([^2H_6]DMSO)$ 7.07-7.55 (6H, m), 7.72 (5H, s) and 8.90 (1H, s) ppm, one NH exchanged with solvent, $\delta C([^2H_6]DMSO)$ 120.7, 123.5, 128.19, 128.49, 130.1, 130.73, 133.76, 138.88, 148.84, 165.0 and 181.5 ppm.

The filtrate after removal of yellow substance, was neutralised with sodium hydroxide, a light yellowish solid was obtained. Recrystallisation from hot acetone gave (102a).

M.p. 220°, mixed m.p. 220°, m/e 403 (M^+), ν_{max} 3380 (NH), 1600 (C=N) and 1060 (C=S), $\delta C([^2H_6]DMSO)$ 119.94, 120.51, 122.62, 128.04, 128.37, 128.87, 130.08, (119.94-130.08, protonated aromatic carbons, m), 135.01 (s), 139.36 (s),

139.78 (s), 147.79 (s), 178.2 (s) and 184.2 (s) ppm.

(Found: C, 62.51; H, 4.03; N, 17.55 $C_{21}H_{17}N_5S_2$ requires C, 62.50; H, 4.24; N, 17.35%)

CHAPTER 5

Structure elucidation of Hector's Base, Dost's Base, and related compounds by nitrogen-15 and carbon-13 nmr spectroscopy

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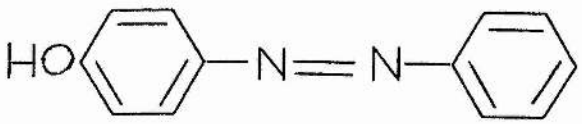


131

INTRODUCTION

Oxidation of alkyl and aryl derivatives of thioureas as described in Chapter 4 yields a 1,2,4-thiadiazole ring system. The positions of peripheral substituents (alkyl and aryl groups) around the thiadiazolidine ring are so confusing that one is uncertain of the structures of the products resulting from the oxidation of thioureas. However, in this chapter, we have attempted to elucidate the structures of Hector's Base, Dost's Base, and related compounds by nitrogen-15 and carbon-13 nmr spectroscopy.

We have also found that Hector's Base forms addition products with methyl isothiocyanate, phenyl isothiocyanate, methyl and phenyl isocyanates, and in all these cases a prototropic shift occurs. Dimethylated Hector's Base, where the prototropic shift is not possible, does not form adducts with these reagents. However, it does form an adduct with 4-nitrobenzendiazonium tetrafluoroborate, but not with benzenediazonium tetrafluoroborate, which is difficult to explain. In addition to this, it has also been found that, during reaction, benzenediazonium tetrafluoroborate decomposes into 1,4-diphenylbenzene (130) and 4-hydroxyazobenzene (131) while 4-nitrobenzenediazonium tetrafluoroborate remains intact.

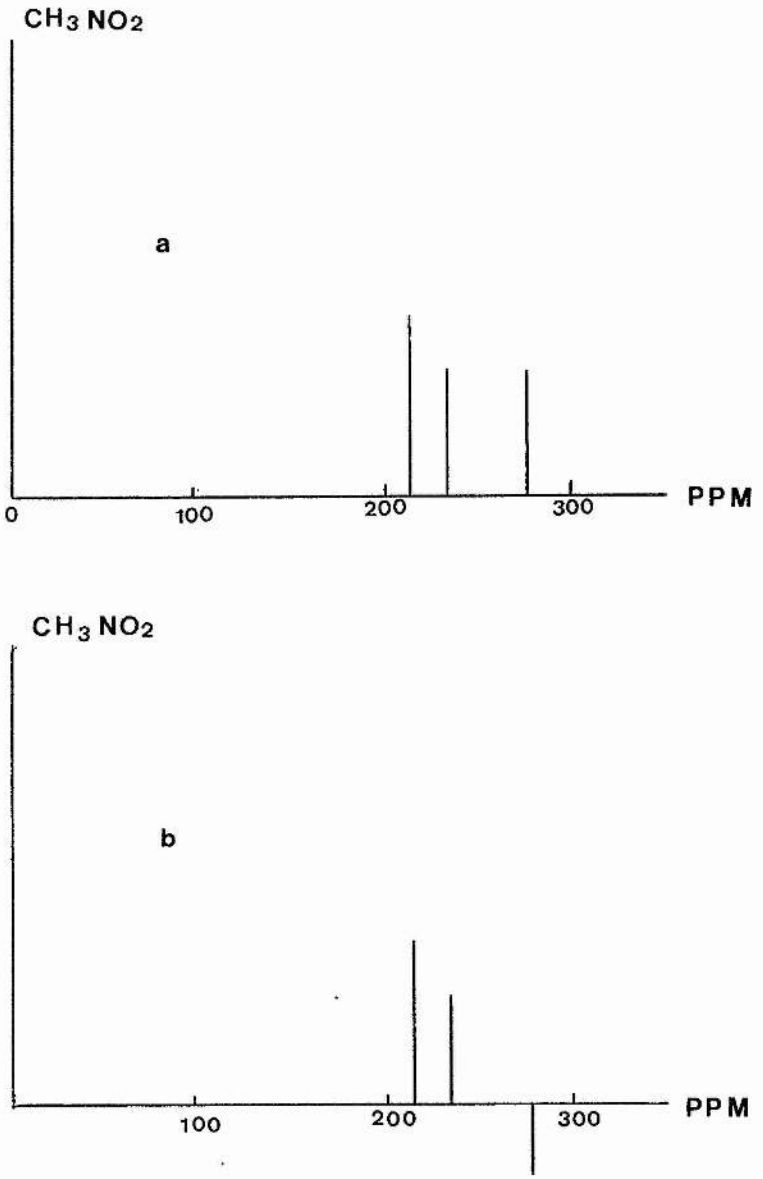
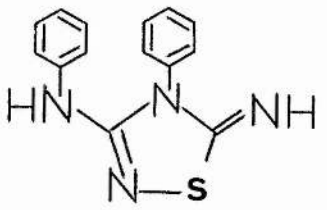


FIG 4 (a) Gated and (b) Nongated ^{15}N nmr Spectra of Dost's Keto-Compound



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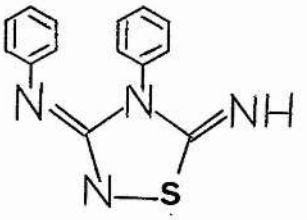

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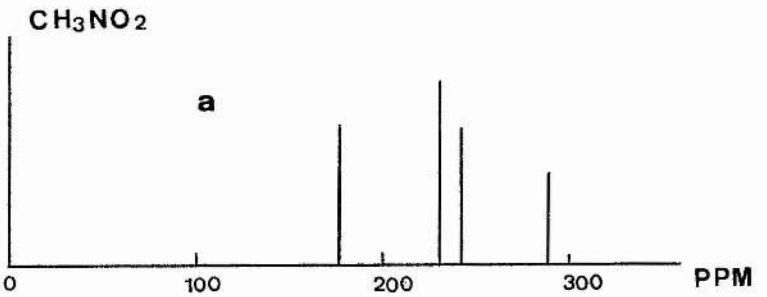

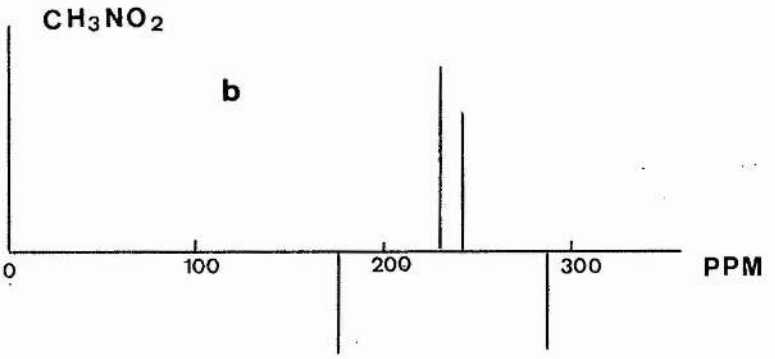

FIG 3 (a) Gated and (b) Nongated ^{15}N NMR SPectra of Hector's Base

RESULTS AND DISCUSSION

An X-ray study (Glidewell et al, 1978) has shown that, in the crystalline state, Hector's Base has structure (76). Previous to this study the generally favoured structure, based on chemical evidence, was (73) (Kurzer and Sanderson, 1962). Structures (76) and (73) differ only in the position of one of the hydrogens and one of the double bonds. However, it is possible that, on solution, Hector's Base undergoes a prototropic shift and that (73) is the form of the molecule in solution. We examined this possibility by the use of nitrogen-15 nmr spectroscopy.

The gated and nongated spectra of Hector's Base in DMSO solution are shown in Figure 3 . In the nongated spectrum the resonance of hydrogen-bearing nitrogens becomes inverted and so the two hydrogen bearing nitrogens of Hector's Base must have the two outermost chemical shifts (δ -288.1 and -183.8 ppm relative to external nitromethane). It is difficult to deduce more from the spectra of a single compound. Fortunately there are a number of related compounds and examination of their spectra permits further deduction.

Dost's keto-compound (Dost, 1906) is prepared from Hector's Base by reaction with aqueous acid. Its structure in the crystal is known to be (117) (Glidewell et al, 1979). The gated and nongated nitrogen-15 nmr spectra are very similar to those of Hector's Base (Figure 4), except that the resonance at δ -183.81 ppm is missing. This correlates the exocyclic imino nitrogen of Hector's Base with this chemical shift. Also, the similarity of the rest of the spectra

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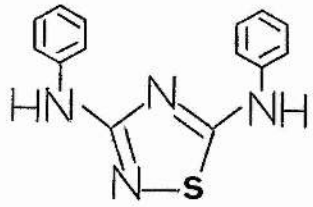

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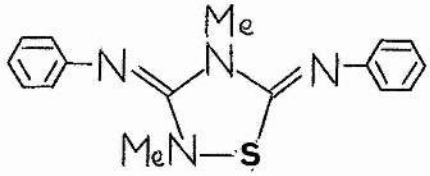

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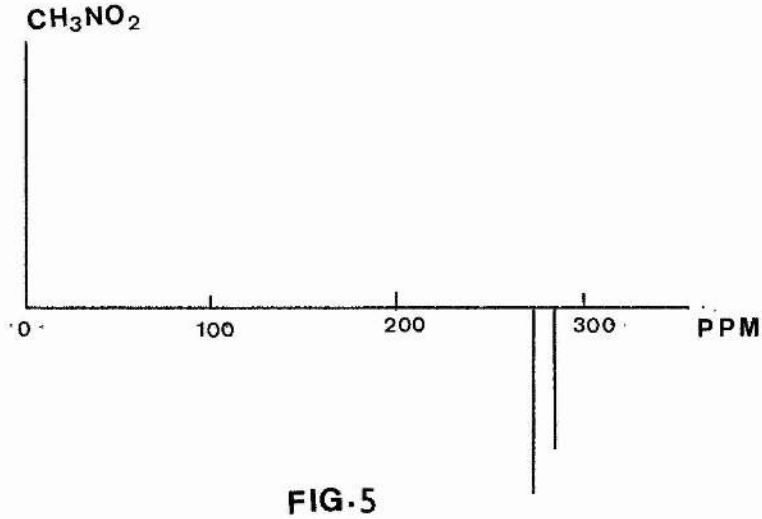


FIG.5

Nongated ^{15}N nmr SPectrum of Dost's Base

of Hector's Base and Dost's keto-compound indicates that the molecules have similar structures, ie. if Hector's Base is (76) then Dost's keto-compound is (117), but if Hector's Base is (73) then Dost's keto-compound is (118). A hydrogen-bearing nitrogen with a chemical shift of around -290 ppm does favour structures (76) and (117). The nitrogen of aniline, in carbon tetrachloride solvent, has a chemical shift of 325.9 ppm (Lichter and Roberts, 1974). The puzzling feature of both sets of spectra is the similarity in the shifts of the other two nitrogen.

Further illumination comes from an examination of the spectrum of Dost's Base, which is made by the rearrangement of Hector's Base in ammonical ethanol at 120°. There are four possible structures (119-121 and 77) for this compound, differing only in the positions of hydrogens. The generally accepted structure is (119) (Kurzer, 1965) but, in view of the known crystal structure of Hector's Base, this is unlikely. The nongated nitrogen-15 nmr spectrum is shown in Figure 5. Clearly the two hydrogen-bearing nitrogens in Dost's Base are very similar and that points to (77) or, possibly, (119). The chemical shifts of these nitrogen atoms (δ -277.5 and 280.9 ppm) are similar to that of the hydrogen-bearing nitrogen common to Hector's Base and Dost's keto-compound. There is one other nitrogen (not bearing a hydrogen) which has a similar chemical shift in all three compounds (δ -211.6, -233.2 and -229.8 ppm). This points to another common structural feature in all three compounds.

All the data are consistent with structures (76), (117) and (77). Compound (74), the structure of which is known from X-ray study

TABLE 2

^{13}C nmr spectra of some heterocycles related to Hector's Base

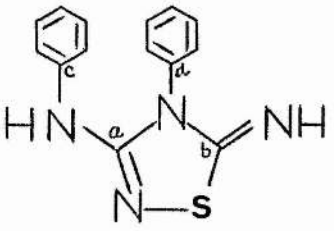
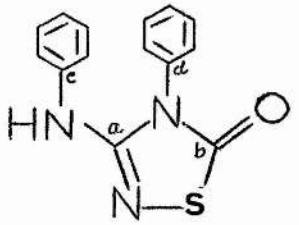
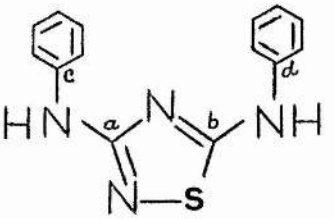
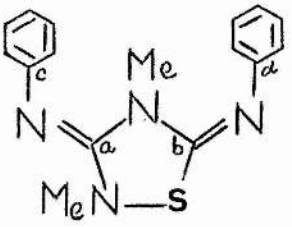
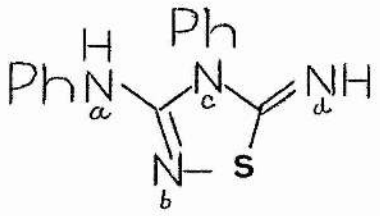
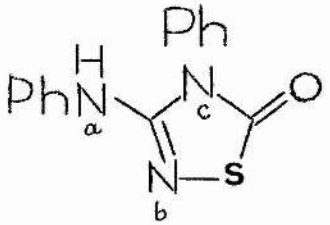
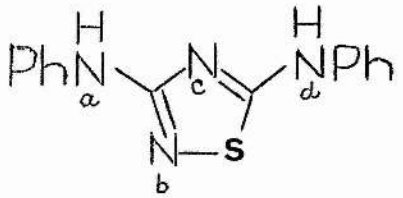
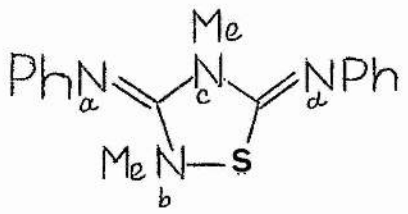
	Solvent	Chemical shift in ppm C(a)	C(b)	C(c)	C(d)
 76	DMSO	147.6	164.6	133.8	139.1
 117	DMSO	147.6	175.6	132.7	138.7
 77	DMSO	162.3	176.3	140.7	141.8
 74	$CHCl_3$	147.5	153.5	149.5	149.1

TABLE 1

^{15}N nmr spectra of some heterocycles related to Hector's Base

	Solvent	Chemical shift in ppm N(a)	N(b)	N(c)	N(d)
 76	DMSO	-288.1	-233.3	-230.5	-183.8
 117	DMSO	-287.3	-229.8	-216.9	-
 77	DMSO	-280.9	-211.6	-147.7	-277.5
 74	$CHCl_3$	-186.7	-330.2	-255.8	-146.6

(Christophersen et al, 1975), is included for comparison. Here both double bonds are exocyclic and the chemical shifts are sufficiently different to provide negative proof of the proposed structures (76), (117) and (77). All the data are displayed in Table 1.

Nitrogen (b) is common to the first three compounds and we see a similar chemical shift. Nitrogen (d) in (76) has a chemical shift similar to that of the imino group (=NH) in dimethylguanidine (δ -207.8 ppm) (Witanowski et al, 1976). The similarity in chemical shift of nitrogens (b) and (c) in both (76) and (117) must be fortuitous. The change in chemical environment of nitrogen (c) in Dost's Base produces a large change in the chemical shift. The conclusion is that, for this type of compound, the factors which govern the molecular structures are the same in solution as in the crystal.

The principal resonances in the carbon-13 nmr spectra of the above four compounds are given in Table 2. They are all consistent with the structures proposed. The chemical shifts for Hector's Base were reported by Akiba et al (1976).

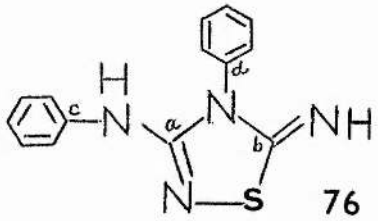
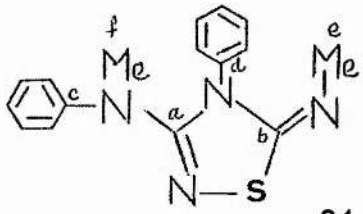
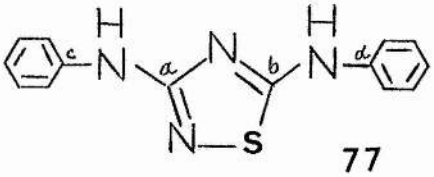
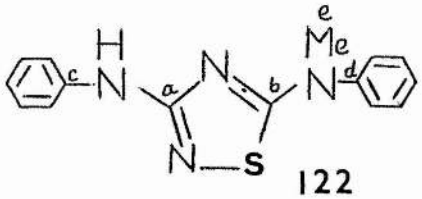
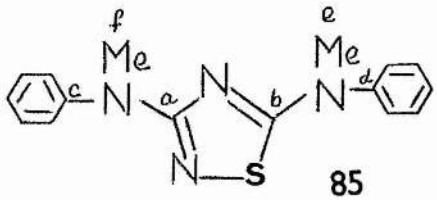
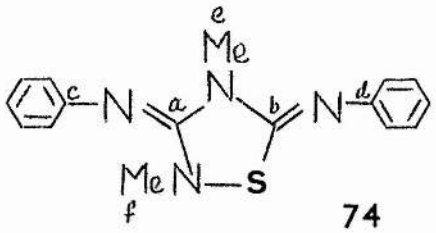
For synthetic reasons, which will be explained later, we wished to prepare Hector's Base with the two exocyclic nitrogens methylated. It was also of interest to see if the methyl group appeared at the same position as the departing hydrogen, or if a prototropic shift occurred prior to reaction. The only reagent which effected methylation was iodomethane and sodium hydride in DMF.

119

101

TABLE 3

^{13}C nmr spectra of methylated Hector's and Dost's Bases

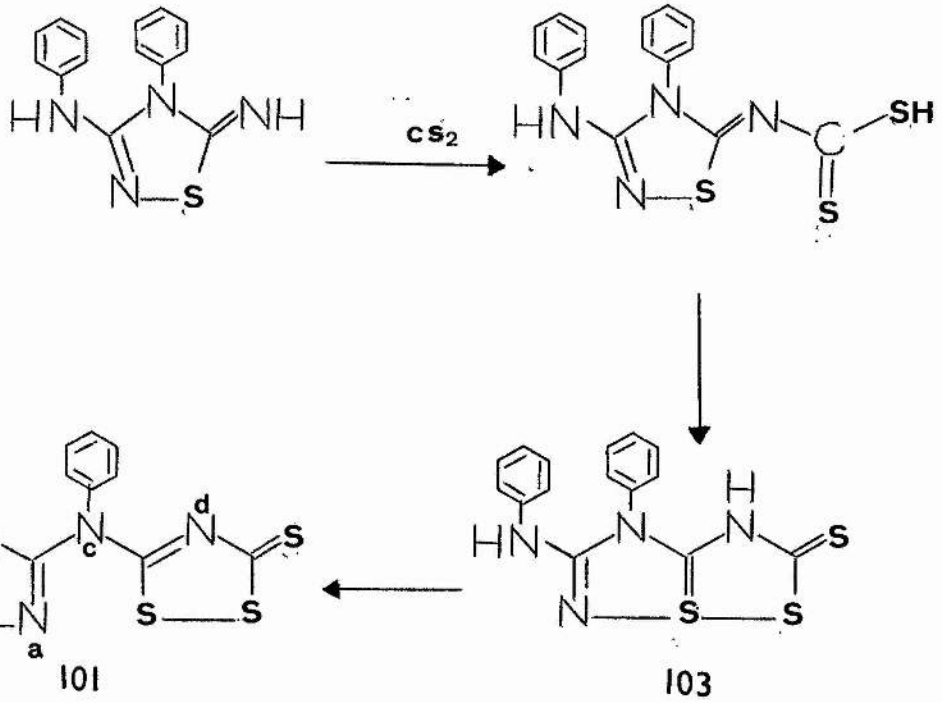
	Chemical shift in ppm					
	Solvent	C(a)	C(b)	C(c)	C(d)	C(e)	C(f
 76	DMSO	147.6	164.6	133.8	139.1	-	-
 84	$CHCl_3$	155.3	163.8	136.0	145.6	40.0	41.
 77	DMSO	162.3	175.3	140.7	141.8	-	-
 122	$CHCl_3$	162.4	181.2	140.2	144.9	40.6	
 85	$CHCl_3$	166.1	182.8	144.8	146.0	40.3	38.
 74	$CHCl_3$	149.5	153.5	147.5	149.1	40.0	31.

The principal carbon-13 nmr chemical shifts of the product are displayed in Table 3. Dimethylated Hector's Base appears to have structure (84) as methylation produces only small changes in the chemical shifts observed for Hector's Base itself. We were unable to obtain an nitrogen-15 nmr spectrum.

In the methylation of Dost's Base (77) we were able to isolate both the monomethylated and dimethylated compounds. Examination of the figures in Table 3 shows that monomethylation leaves one half of the molecule unaffected C(a) and C(c). This suggests structure (122) and this assignment is confirmed by the nitrogen-15 nmr spectrum. N(a) of Dost's Base (see Table 1) remains inverted in the nongated spectrum of (122) (δ -283.4 ppm) while N(d) is no longer inverted (δ -291.0 ppm) and must be methylated. However, the chemical shifts are not greatly changed. The same is true of N(b) and N(c) (δ -209.8 and -151.2 ppm) and so monomethylation of Dost's Base retains the basic molecular structure.

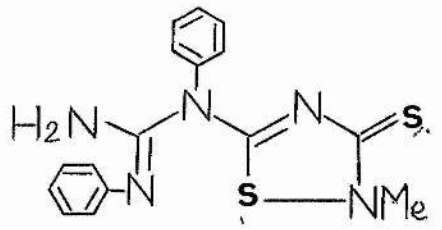
The carbon-13 nmr spectrum of dimethylated Dost's Base indicates that the second methylation occurs of N(a) and, therefore, the structure must be (85). If methylation of Dost's Base in the form of (119) had occurred, then the product would have been (74), but the data in Table 3 demonstrate that (85) and (74) differ in structure. This is further evidenced for the proposed structure of Dost's Base.

Hector's Base reacts with a number of compounds to give adducts. The adduct with carbon disulphide has structure (101) in the crystal (Glidewell et al, 1978). The kinetics of reactions

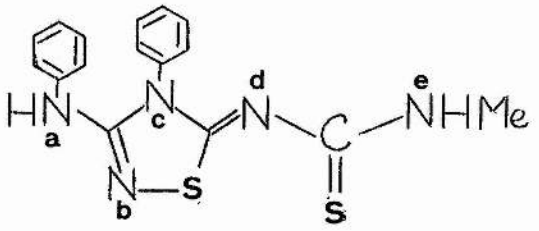


SCHEME 22

123



124



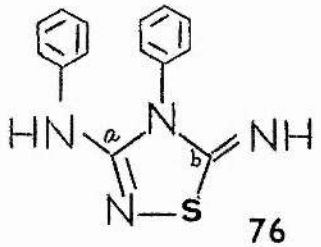
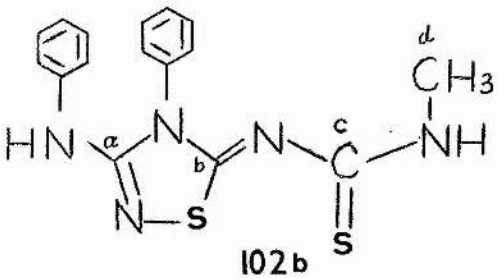
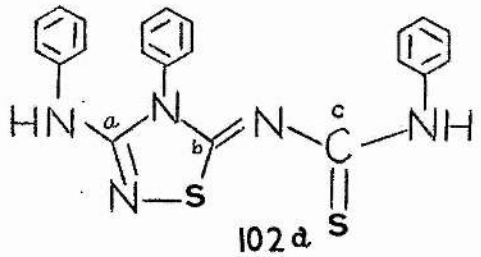
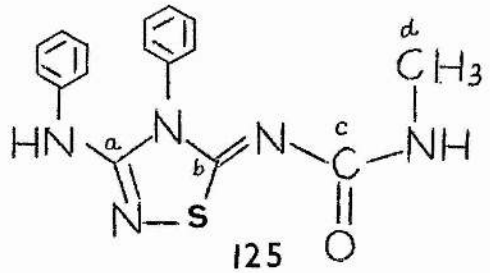
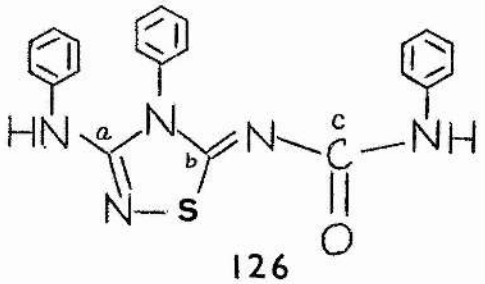
102 b

(Butler, 1978) and the nature of the product lead us to suggest a mechanism for reaction shown in Scheme 22, with a bicyclic intermediate (103). There is no reaction with dimethylated Hector's Base. Similar 'bond switches' in adducts formed with Hector's Base have been reported by Akiba et al (1976). The nitrogen-15 nmr chemical shifts for (101) are δ -94.4, -197.8, -234.2 and -306.5 ppm, very different from those of Hector's Base, but consistent with the extensive rearrangement which has occurred. In the nongated spectrum of (101) the last is inverted, so this corresponds to N(b). By its similarity with N(c) of Hector's Base I think that N(c) of (101) has a shift of δ -234.2 ppm, and therefore N(a) and N(d) have shifts of δ -197.8 and -94.4 ppm.

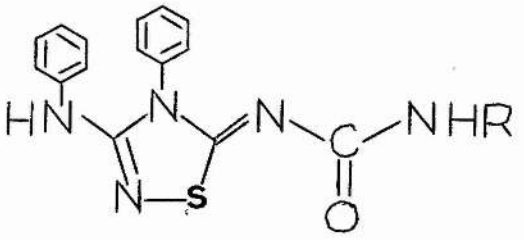
Methyl isothiocyanate is closely related to carbon disulphide and also forms an adduct with Hector's Base. If the reaction parallels that shown in Scheme 22, then either an S-S or S-N bond could form to give (123) or (124). We were unable to predict with any certainty which would form. In fact, neither formed. An X-ray study showed the structure at the adduct to be (102b) (Glidewell et al), We propose a compound of this type as the first intermediate in the reaction of carbon disulphide with Hector's Base (See Scheme 22). For some reason, which we cannot discern, reaction with methyl isothiocyanate stops at this stage. The chemical shifts in the nitrogen-15 nmr of (102b) are δ -288.1, -251.4, -218.1, -199.6, and -151.3 ppm, which, by comparison with the spectrum of Hector's Base, we assign to N(a), N(e), N(c), N(b) and N(d) of (102b). The nitrogen-15 nmr spectrum confirms the evidence of the X-ray study that extensive molecular rearrangement has not occurred. Similar

TABLE 4

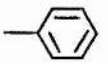
^{13}C nmr spectra of some adducts of Hector's Base

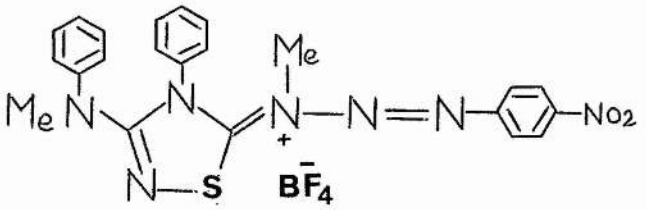
	Solvent	Chemical Shift in ppm C(a)	C(b)	C(c)	C(d)
 76	DMSO	147.6	164.6	-	-
 102b	DMSO	147.7	175.7	178.6	31.4
 102d	DMSO	147.8	178.2	184.2	-
 125	DMSO	146.8	174.2	163.5	39.3
 126	DMSO	147.4	175.8	161.4	-

102a

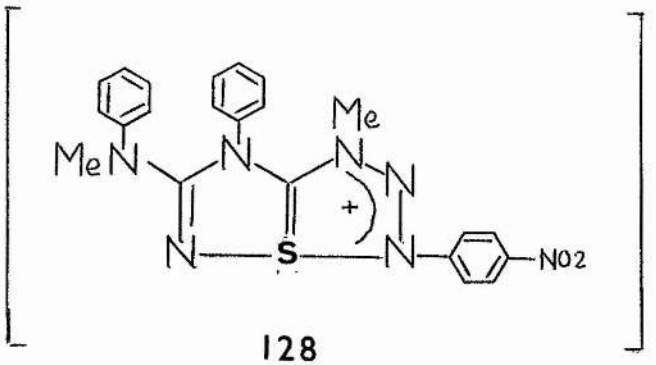


125 R = Me

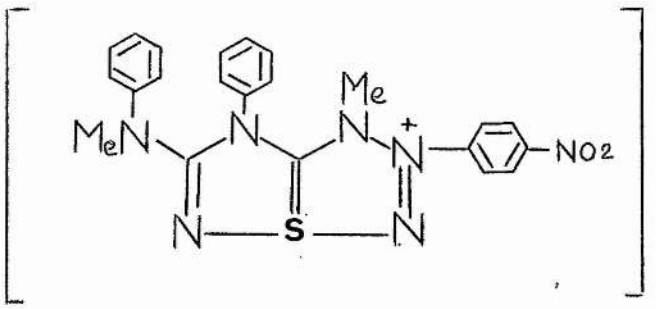
126 R = 



127



128



129

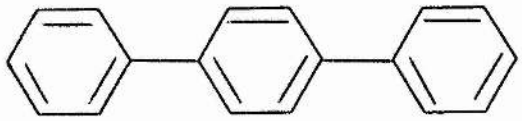
adducts were prepared from phenylisothiocyanate (102a), methyl isocyanate (125) and phenylisocyanate (126). The similarity of structure for these adducts is deduced from the carbon-13 nmr spectra, displayed in Table 4. None of the above reagents reacts with dimethylated Hector's Base, which confirms the prototropic shift necessary for the formation of (102), (125) and (126).

Bicyclic compounds with a 'hypervalent' sulphur atom like (103) are a known class of compounds (Lozac'h, 1971). We sought an electrophile which reacts with Hector's Base where reaction goes beyond simple addition (as with methyl isothiocyanate) but does not result in ring opening (as with carbon disulphide). We think that the 4-nitrobenzenediazonium ion is such an electrophile. On mixing Hector's Base and 4-nitrobenzenediazonium tetrafluoroborate in acetronitrile an intensely coloured solution results. Removal of solvent yielded a crimson tar which we were unable to induce to crystallise. However, with dimethylated Hector's Base crimson crystals were obtained. The structure of this product proved difficult to elucidate. It cannot be equivalent to (101) as there is no mobile hydrogen on N(d). We are left with three possibilities (127)-(129). If a 'hypervalent' sulphur does form then (129) is unlikely as (128) has greater resonance stability. The only diagnostic features of the ir spectrum were a C=N stretching band at 1570 cm^{-1} and absorbances characteristic of the BF_4^- ion. The proton nmr spectrum was only a little more informative: two NMe groups in rather different environments and a complex of aromatic protons. The methyl groups appear in the carbon-13 nmr

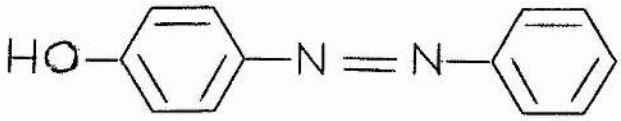
spectrum at δ 33.6 and 43.1 ppm, by comparison with the figures for the methyl groups of methylated Hector's Base (Table 2), it is seen that one of them has experienced an up-field shift. The other three tertiary carbons have chemical shifts at δ 143.6, 156.0, and 178.6 ppm. Although I would not care to assign these chemical shifts, they are significantly different from those of methylated Hector's Base (Table 3) and suggest that the ring structure has been seriously disturbed ie. (128) rather than (127).

The nitrogen-15 nmr spectrum of this compound was of special interest in that there are seven different nitrogen atoms. Unfortunately for the diagnosis of structure, there were only five peaks in the observed spectrum. We are unable to explain this effect. Apart from the chemical shift at low field, which was obviously due to the nitrogen of the nitro-group, we were unable to assign the peaks that were obtained. One of the peaks at δ -286.6 ppm was inverted. This is difficult to explain as none of the nitrogens is hydrogen-bearing. Thus, the nitrogen-15 nmr spectrum was of no value in choosing between (127) and (128).

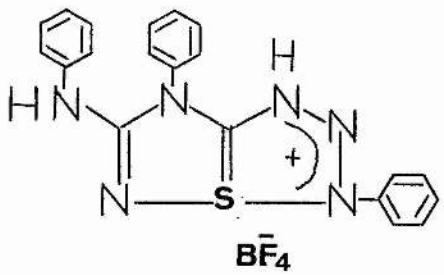
The last piece of evidence we present to support (128) is also spectral. There is strong absorption in the uv/visible spectrum, which is characteristic of compounds like (128) (Reid, 1973). However, we recognise that the combination of a nitro-group and the diazo-group could also be the origin of this absorption. No single piece of spectral evidence is fully diagnostic but we believe that <u>in toto</u>, structure (128) is favoured. The material does not



130



131



132

crystallise well and so it is unlikely we will ever have the ultimate assurance of a crystal structure.

Similarly, benzenediazonium tetrafluoroborate which seems to be less electrophilic than its 4-nitro isomer was also tried with Hector's Base. In this case evolution of nitrogen gas was found and three products, after column chromatography, were isolated. The first two products were 1,4-diphenylbenzene (130) and 4-hydroxyazobenzene (131) and the last one was an adduct (132) of Hector's base. Compound (132) is a yellow solid which melts at 298°. Its mass spectrum did not provide any useful information, but elemental analysis suggested a molecular formula of $[C_{20}H_{17}N_6S]^+BF_4^-$. The proton nmr spectrum was only a little more informative: two multiplets at δ 7.12-7.50 and 7.74-7.84 ppm which corresponded to aromatic protons of 10 and 5. The noise-decoupled and off-resonance carbon-13 nmr spectra favoured a structure (132) without methyl groups, which is analogous to (128), in addition to (127) and (129). The ir spectrum indicated the presence of NH and BF_4^- groups.

I believe that formation of compounds (130) and (131) came from the result of decomposition of benzenediazonium tetrafluoroborate in DMF. The phenyl radical so formed trimerise to give (130) and has picked up an hydroxyl group to yield phenol. The diazonium ion and phenol couple together to afford (131), which is, of course, a well known reaction in the formation of diazo compounds. Both compounds (130) and (131) were identified by comparison with autentic samples and by spectral means.

Surprisingly, dimethylated Hector's Base did not react with benzenediazonium tetrafluoroborate but gave compounds (130) and (131). These two compounds were also obtained when benzenediazonium tetrafluoroborate in DMF alone, under same experimental conditions as we used in above cases, was stirred for 24 h. It was found that liberation of nitrogen gas from the reaction of Hector's Base and dimethylated Hector's Base with benzenediazonium salt was more than from the diazonium ion alone. This is difficult to explain. It is probably due to the presence of hydrogen at exocyclic nitrogen of Hector's Base. There was no evolution of gas in case of 4-nitrobenzenediazonium tetrafluoroborate with Hector's Base and dimethylated Hector's Base reactions.

EXPERIMENTAL

a) Hector's Base (76) was prepared by the oxidation of 1-phenylthiourea by hydrogen peroxide (Kurzer and Sanderson, 1959).

M.p. 183°, $\delta N(^2H_6]DMSO)$ -183.8, -230.5, -233.3, and -288.1 ppm.

b) Oxidation of 1-(N,N-dimethylamidino)-3-phenylthiourea (Kurzer and Taylor, 1962) gave Dost's Base (77).

M.p. 201°, $\delta C(^2H_6]DMSO)$ 117.04-129.19 (m), 140.01 (s), 141.14 (s), 162.31 (s), and 176.52 (s), $\delta N(^2H_6]DMSO)$ -147.7, -211.6, -277.5 and -280.9 ppm.

c) Oxidation of 1-methyl-3-phenylthiourea with nitrous acid gave (74) (Christophersen et al, 1975).

M.p. 132° (lit. 125°, Christophersen et al, 1975), $\delta C(CDCl_3)$ 31.7, 40.0, 121.0-129.5, 147.5, 149.1, 149.5 and 153.5, $\delta N(CDCl_3)$ -146.6, -186.7, -255.8 and -330.2 ppm.

d) Hector's Base (5.1 g) was added a little at a time to a solution of dry sodium hydride (1.0 g) in dry DMF (30 ml). After cooling in an ice bath iodomethane (8 ml) was added with stirring. After standing for 2 h. the mixture was poured into water and the precipitate filtered off. Dimethylated Hector's Base (84) was crystallised from chloroform.

M.p. 150°, m/e 296 (M^+), ν_{max} (mull) 1640 (C=N) 1585 and 1555 cm^{-1} (aromatic C=C), $\delta H(CDCl_3)$ 2.90 (3H, s), 3.18 (3H, s),

and 6.70-7.14 (10H, m), $\delta C(CDCl_3)$ 40.0 (q), 41.3 (q), 123.8-128.7 (m), 136.0 (s), 145.6 (s), 155.3 (s) and 163.8 (s). In spite of over 600,000 scans and addition of a relaxant we could not observe any resonance in the ^{15}N nmr spectrum. (Found: C, 64.49; H, 5.23; N, 18.69. $C_{16}H_{16}N_4S$ requires C, 64.85; H, 5.44; N, 18.90%)

e) Dost's Base (2.68 g) was dissolved in dry DMF (30 ml) and cooled to -5°. Sodium hydride was added a little at a time with stirring. When evolution of hydrogen had ceased, iodomethane (5 ml) was added and the mixture stirred for 1 h. After pouring into water the precipitate was filtered off. Monomethylated Dost's Base (112) was recrystallised from chloroformm.

M.p. 120°, m/e 282 (M^+), ν_{max} (mull) 3250 (NH) and 1620 cm^{-1} (C=N), $\delta H(CDCl_3)$ 3.50 (3H, s) and 6.90-7.85 (11H, m, addition of D_2O reduced the multiplet to 10H), $\delta C(CDCl_3)$ 40.58 (q), 116.0-132.2 (m), 140.2 (s), 145.0 (s), 162.4 (s), and 181.2 (s), $\delta N(CDCl_3)$ -151.2, -209.8, -283.3, and -291.0 ppm (Found: C, 63.87; H, 5.10; N, 19.60 $C_{15}H_{14}N_4S$ requires C, 63.80; H, 4.99; N, 19.84%)

f) The above was repeated using double the quantity of sodium hydride and stirring was continued for overnight. A yellow oil was obtained. This was dissolved in a 1:1 chloroform-acetone mixture and, on evaporation at room temperature, yellowish crystals were obtained. They were filtered off and washed with a small amount of ethylacetate and acetone in order to remove yellow gum. Dimethylated Dost's Base (85).

M.p. 94°, m/e 296 (M^+), ν_{max} (mull) 1600 cm^{-1} (C=N), $\delta H(CDCl_3)$ 3.42 (3H, s), 3.50 (3H, s), and 7.14-7.46 (10H, m), $\delta C(CDCl_3)$ 38.9 (q), 40.3 (q), 122.4-131.1 (m), 144.8 (s), 146.0 (s), 166.1 (s) and 182.8 (s) ppm. (Found: C, 64.35; H, 5.01; N, 18.86 . $C_{16}H_{16}N_4S$ requires C 64.86; H, 5.40; N, 18.91%)

g) Hector's Base - MeNCS adduct (102b)

MeNCS (2 ml) was added to a solution of Hector's Base (1 g) in hot acetone and the mixture allowed to cool. Yellow crystals were filtered off and recrystallised from acetone.

M.p. 224°, m/e 341 (M^+), ν_{max} (mull) 3280-3380 (NH) and 1570 cm^{-1} (C=N), $\delta C([^2H_6]DMSO)$ 31.4, 119.7-129.8, 134.9, 139.4, 147.7, 175.7 and 178.6, $\delta N([^2H_6]DMSO)$ -151.3, -199.6, -281.1, -251.4, and-288.1 ppm (Found: C, 56.07; H, 4.44; N, 20.56 . $C_{16}H_{15}N_5S_2$ requires C, 56.28; H, 4.43; N, 20.51%)

h) Hector's Base - PhNCS adduct (102a)

The above was repeated using PhNCS to give yellow crystals.

M.p. 220°, m/e 403 (M^+), ν_{max} (mull) 3240-3140 (NH) and 1580 cm^{-1} (C=N), $\delta C([^2H_6]DMSO)$ 119.9-130.1 (m), 135.0 (s), 139.4 (s), 139.8 (s), 147.8 (s), 178.2 (s), and 184.2 (s) ppm (Found: C, 62.34; H, 4.17; N, 17.26 . $C_{21}H_{17}N_5S_2$ requires C, 62.51; H, 4.24; N, 17.36%)

i) Hector's Base - MeNCO adduct (125)

MeNCO (2 ml) was added to a solution of Hector's Base (1 g) in hot acetone and the mixture allowed to cool. The white crystals obtained were recrystallised from acetone.

M.p. 223°, m/e 325 (M^+), δC([$^2H_6$]DMSO) 39.3 (q), 119.6-129.8 (m), 134.5 (s), 139.4 (s), 146.8 (s), 163.5 (s), and 174.2 (s) ppm (Found: C, 58.77; H, 4.45; N, 21.88 $C_{16}H_{14}N_5OS$ requires C, 59.06; H, 4.65; N, 21.52%)

j) Hector's Base - PhNCO adduct (126)

The above was repeated using PhNCO.

M.p. 214°, m/e 387 (M^+), ν_{max} (mull) 3380, 3250 (NH) and 1700 cm^{-1} (C=O) δC([$^2H_6$]DMSO) 118.2-130.1 (m), 134.4 (s), 139.4 (s), 140.0 (s), 147.4 (s), 161.4 (s) and 175.8 (s) ppm. (Found: C, 64.77; H, 5.11; N, 15.89 $C_{21}H_{17}N_5OS$ requires C, 65.10; H, 5.15; N, 15.49%)

k) Hector's Base - 4-Nitrobenzenediazonium tetrafluoroborate adduct (128)

Dimethylated Hector's Base (1 g) and 4-nitrobenzenediazonium tetrafluoroborate (Vogel, 1978) (1 g) were dissolved in acetonitrile (100 ml) and stirred for 2 h at room temperature. The solvent was removed and ethanol added to the residue. The deep red crystals were recrystallised from dichloromethane.

M.p. 130-140° (dec.), ν_{max} (mull) 1570 (C=N), 1080, 850, and 770 cm^{-1} (BF_4^-), 380, 3980, δH($CDCl_3$), 3.00 (3H, s), 3.26 (3H, s),

and 6.66-7.26 (14H,m), $\delta C(CDCl_3)$ 33.6 (q), 43.1 (q), 123.8-132.3 (m), 143.6 (s), 156.0 (s) and 178.6 (s), $\delta N(CDCl_3)$ -15.5, -209.8, -221.8, -286.6, and -303.6 ppm (Found: C, 50.14; H, 3.96; N, 16.80 $C_{22}H_{20}N_7O_2SBF_4$ requires C, 49.55; H, 3.77; N, 18.38%)

There was no reaction of dimethylated Hector's Base with CS_2 and MeNCS.

1) Hector's Base - Benzenediazonium tetrafluoroborate adduct

Hector's Base (2.68 g) and benzenediazonium tetrafluoroborate (3 g) in DMF were stirred overnight at room temperature. Nitrogen gas was liberated. After that, chloroform (200 ml) was added and then whole contents were washed with water in order to remove unreacted diazonium salt and DMF. After solvent removal, the residue was treated with column chromatography (Al_2O_3). The column was washed with ether, chloroform and acetone respectively. Ether extraction gave white crystals contaminated with red gum, which was removed by washing with methanol gave colourless crystals of 1,4-diphenylbenzene (130).

M.p. 209° (lit. 209°, 213°, Pollock et al, 1965), m/e 230 (M^+). Other properties are identical to authentic sample.

Chloroform extraction gave red liquid which yielded deep orange crystals of 4-hydroxyazobenzene (131) after keeping for a long time.

M.p. 152° (lit. 152°, Pollock et al, 1965), m/e 198 (M^+), ν_{max} (mull) 3120-40 (OH) and 1585 cm^{-1} (N=N), $\delta C([^2H_6]acetone)$ 116.59, 123.07, 125.63, 129.81, 130.99, 147.06, 153.50 and 161.31 ppm (Found: C, 72.94; H, 4.91; N, 13.98 $C_{12}H_{10}N_2O$

requires C, 72.71; H, 5.08; N, 14.13%)

Acetone effluent gave a yellow solid (132) which was recrystallised from methanol.

M.p. 298°, ν_{max} (mull) 3400-3180 (NH) and 1580 cm^{-1} (C=N) $\delta H([^2H_6]DMSO)$ 7.12-7.50 (10H, m) and 7.74-7.84 (5H, m), $\delta C[(^2H_6]DMSO)$ 120.85, 123.41, 128.47, 129.04, 130.83, 133.84 (s), 138.62 (s), 149.53 (s) and 178.28 (s) ppm. (Found: C, 51.02; H, 3.55; N, 18.43 $C_{20}H_{17}N_6SBF_4$ requires C, 52.19; H, 3.72; N, 18.25%) λ_{max} (CH_3OH) 400, 308, 254 and 206 nm.

Dimethylated Hector's Base did not react with benzenediazonium tetrafluoroborate. In this case and in a blank experiment (without Hector's Base), compounds (130) and (131) were obtained under the same conditions as we used above.

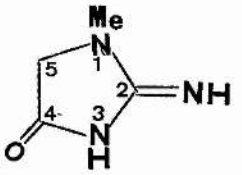
CHAPTER 6

Reaction of an alkaline solution of picric acid with creatinine, hydantoin, and pyruvic acid

INTRODUCTION

In this chapter we have attempted to unfold the complicated story of the Jaffé reaction ie. the reaction of picric acid and creatinine in alkaline media. This reaction gives a red colouration which has been used for many years in the quantitative determination of creatinine present in biological fluids. We have isolated a red solid from the reaction mixture, which is responsible for the colouration and have established its structure by the application of spectral techniques. Besides this, the reaction of an alkaline solution of picric acid with hydantoin and pyruvic acid have also been examined.

Moreover, the behaviour of picric acid and creatinine in neutral and alkaline media has been thoroughly studied by the use of proton and carbon-13 nmr spectroscopy. We have found that creatinine in alkaline media behaves as a molecule with two nucleophilic centres ie. carbanion and imino ($=\bar{N}$) anions are both involved in the formation of the red solid and no H/D exchange occurs in the case of picric acid. A reaction mechanism for the Jaffé reaction has been proposed.



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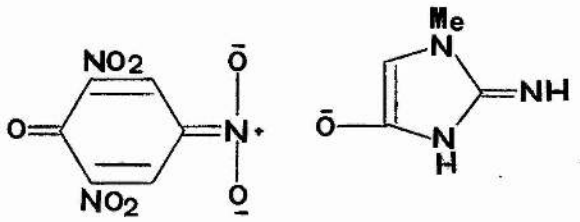

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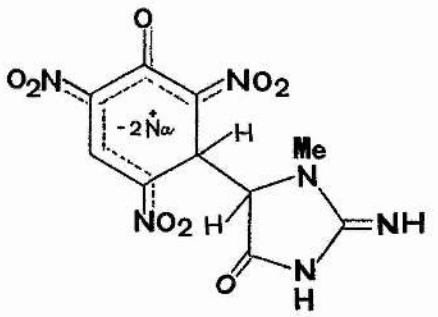
RESULTS AND DISCUSSION

Jaffé (1886) reported that addition of creatinine (2-imino-1-methylimazolidin-4-one) (133) to an alkaline solution of sodium picrate results in formation of a red colour. This reaction was adopted by Folin (1904) as a method for the quantitative estimation of creatinine in biological fluids, but the nature of the red species formed in the reaction has never been determined with certainty. Greenwald and Gross (1924) suggested that it is a tautomer of creatinine picrate but did not specify the exact structure of the tautomer. They found that one mole of picric acid appears to be required for each mole of creatinine, but the full chromogenic value of the creatinine develops in the presence of an excess of picric acid. They roughly estimated that 2.5 moles of picric acid are needed for each mole of creatinine. Later, Greenwald (1928) isolated a red solid from the reaction mixture and postulated both 1:1 and 2:1 complexes of creatinine and picric acid. This red solid was quite different from the picrate, but he reasserted his previous views that formation of red coloured tautomer of creatinine-picrate was the cause of colour. Bollinger (1936) obtained a red solid which analysed as a complex of one mole of picric acid, one mole of creatinine and two moles of sodium hydroxide. Seelig (1969), from spectroscopic and chromatographic studies, showed that the red species is not picramic acid and Seelig and Wüst (1969) proposed structure (134). Similar species have been detected by Bernasconi (1970) in the reaction of amines with polynitro compounds, but they have a very short life-time (a few micro-seconds) and it seems unlikely that (134) is the correct



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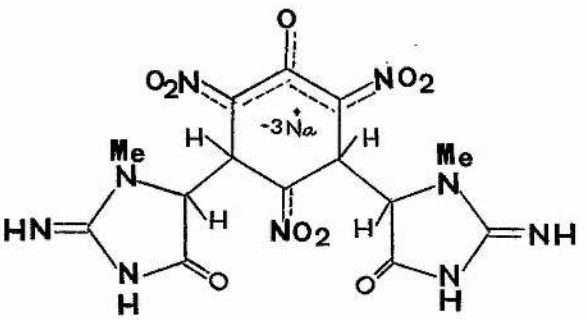

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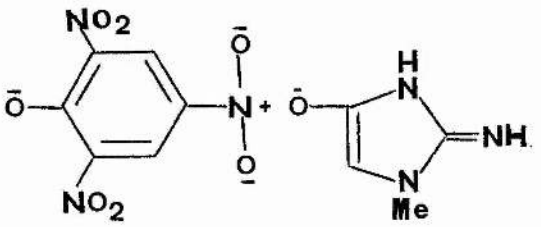

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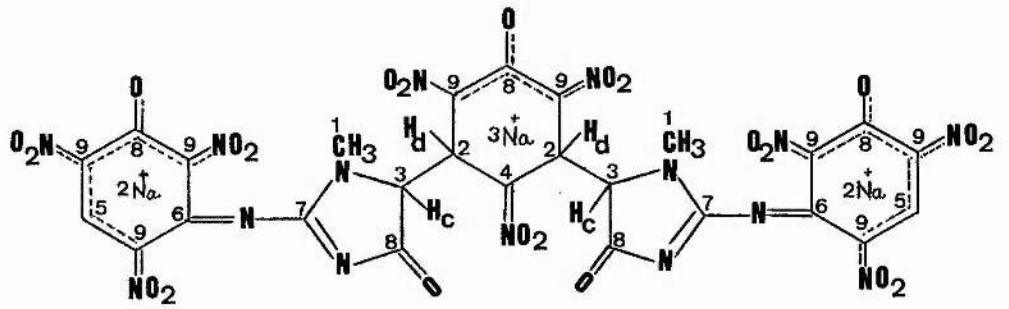
structure. Butler (1975) claimed that red species formed in the Jaffé reaction was the result of attack by the creatinine anion at the unsubstituted position of picrate ion to give 1:1 and 2:1 complexes (135, 136). Recently, Vasiliades (1976), on the basis of spectrophotometric, kinetic and nuclear magnetic resonance studies, tried to prove that alkaline picrate and creatinine react to form a 1:1 adduct. He proposed structure (137) in addition to (134), but the spectroscopic evidence given in their support are inconsistent with (137) and (134).

We have found that picric acid reacts with creatinine in alkaline media to afford a bright red substance (138) which does not melt at all. It does not show a molecular ion peak and we cannot deduce anything from its mass spectrum. This failure may be due to its being an involatile salt. However, on the basis of elemental analysis and spectroscopic evidence we suggest a molecular formula of $C_{26}H_{12}N_{15}O_{23}Na_7$ for (138). Compound (138) is highly hygroscopic in nature and difficult to dry. That is why the percentage of hydrogen found is greater than the required amount. However, after prolonged drying under reduced pressure at 100°C it does not show any absorption above 3000 cm^{-1} which indicates uptake of moisture during sample handling. When it was kept open for sometime at room temperature, it showed a very broad absorption due to the hydroxyl group. Other portion of the ir spectrum (C=O and C=N group] remained consistent. The same problem was encountered during sodium analysis. In the normal way, the percentage of sodium found was 13.6 units but using a dry box technique under nitrogen the value increased



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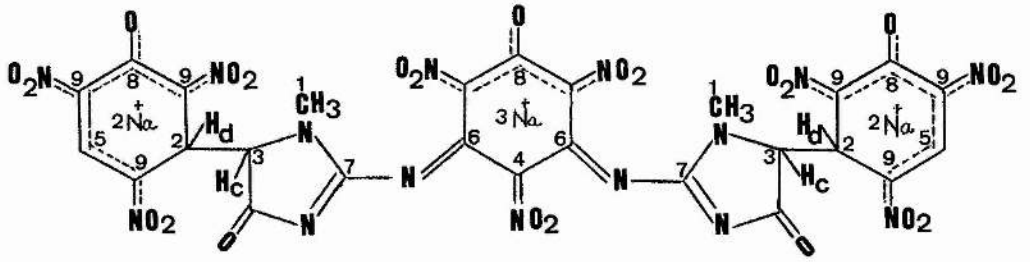

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to 14.15% (required 15.1%). Despite all possible precautions, we could not avoid some moisture absorption, probably during the sample transfer to dry-box. This explains the poor analysis of compound (138).

The proton nmr spectrum in D_2O at 100 MHz using benzene capillary as an external reference shows two singlets at δ 3.61 and 3.96 ppm ($-NCH_3$), one doublet at 3.89 ppm (2 H_c) and two other doublets which are almost overlapping at 6.15 ppm (2 H_d). The singlet at 9.6 ppm is assigned to aromatic protons (2H). The integrated peak areas match well their respective number of protons. In the carbon-13 nmr spectrum two NMe groups (C_1) absorb at δ 30.87 and 31.95, C_2 at 41.59, C_3 at 43.13 and 43.35 ppm, respectively. In the off-resonance spectrum, C_1 splits into quartet, C_2 and C_3 into doublets. The aromatic carbon (C_5) resonates at 127.89 ppm and also exhibits a doublet. A detailed study of spectral data suggests that the structure of compound (138) is symmetrical and a small discrepancy in chemical shifts of C_1 (30.87, 31.95 ppm) and C_3 (43.13, 43.35 ppm) may be the cause by very slight twist in molecule induced by the rotation of C_2-C_3 bond. Similarly, C_7 displays two absorptions at δ 170.00 and 171.93 ppm, and, C_8 three at 188.96, 189.35 and 189.68 ppm respectively. The resonance at 119.38 ppm is unique and is assigned to C_4. Its chemical shift agrees with literature value (Olah and Mayr, 1976) and it remains as a singlet in the off-resonance spectrum which provides an additional proof for the symmetry of molecule (138). Otherwise the picture of the

molecule would have been different. Hence, we assign two structures (138) and (139) to $C_{26}H_{12}N_{15}O_{23}Na_7$, and it is difficult to distinguish between them.

In compound (138) sp^2-carbons containing nitro groups do not appear in the spectrum. Probably, the nitrogen-14 nucleus possesses an electric quadrupole moment, and is, therefore, able to interact with both electric and magnetic field gradients, which cause the nucleus to tumble rapidly, so the spin-lattice relaxation, especially dipole-dipole relaxation, is greatly affected. Since the spin-lattice relaxation time is longer, signals for carbon bearing a nitrogen are either broad or small and sometimes do not appear in the spectrum. Similar effects have also been reported in the case of nitrobenzene (Levy and Nelson, 1972), 1,3,4-trichlorobenzene and other quaternary carbons (Abraham and Loftus, 1979). Despite this, the supression of peak intensity is further aggravated due to the solvent used which adversely affects relaxation phenomena, in addition to changing chemical shift positions.

Hence, we decided to study the carbon-13 nmr spectrum of picric acid and other nitrophenols in different solvents in order to have further insight into the structure of compound (138). Picric acid in DMSO and acetone exhibits four absorptions while in water only one, which is assigned to non-substituted carbon. It changed to a doublet in the off-resonance spectrum (see experimental section). Similar results have also been encountered in the cases of 2,4- and 2,6-dinitrophenols. This observation proves the non-existence of C_9 resonance in the

spectrum of compound (138) and substantiates our proposed structure (138). Conversely, the appearance of C_4 in (138) is surprising, but not unlikely. As Olah and Mayr (1976) reported, in the carbon-13 nmr studies of Meisenheimer complexes of nitro compounds 4-nitro carbon (C_4) relaxed faster than 2-nitro carbon (C_2) because of a small spin-lattice relaxation time, which in turn, confirms the presence of C_4 in the spectrum of (138).

Although the literature reveals that H/D exchange in polynitro compounds is controversial, yet several workers (Buncel et al 1968) have reported that exchange does take place. In order to see this effect the carbon-13 nmr spectra of picric acid in neutral as well as alkaline media were taken. All the carbons absorbed at their right places and no deuterium exchange was found, even keeping the solution for a long time. If the exchange had occurred one should have a triplet by virtue of C-D coupling or at least a hump in addition to a doublet (C-H) in the off-resonance spectrum. But, nothing like this was found and, hence compound (138) remained intact during nmr scanning in D_2O solvent. Despite this, recently Olah and Mayr (1976) reported that there was no exchange of 3-H by deuterium in the studies of Meisenheimer complex resulting from the reaction of 2,4-dinitroanisole and methoxide ion in DMSO-d_6.

A proton nuclear magnetic resonance study of picric acid further endorsed our findings. As mentioned in the experimental section, ring protons in various solvents resonate at their

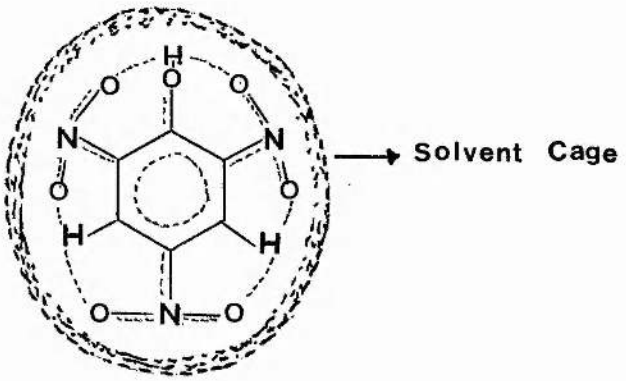


FIG. 6

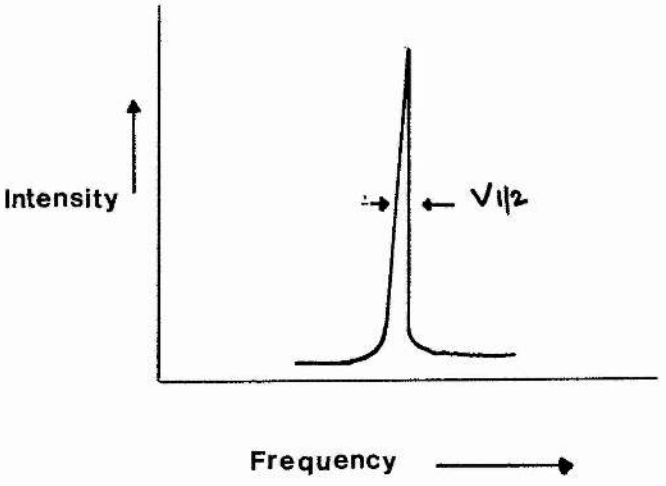
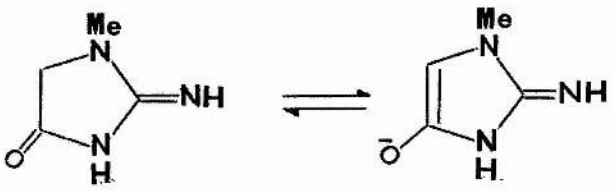


FIG. 7

respective place (small differences in chemical shifts are due to solvent). On addition of a few drops of D_2O the peak intensity was reduced suggesting that the ring protons had exchanged with deuterium. Then the spectrum was recorded in pure D_2O and a very small peak appeared at δ 8.9 ppm. An exactly identical effect was seen when it was scanned in pure H_2O. Moreover, picric acid in an organic solvent containing a few drops of H_2O showed the same behaviour as in an organic-D_2O system. However, on slightly basifying the solution, the peak height was further reduced. These experimental facts rule out the idea of deuterium exchange and suggest solvation effect which could probably, be pictured as in Fig. 6. Ives and Moseley (1966) also reported the abnormal behaviour of picric acid in aqueous media and stressed the importance of solvation phenomena. Besides spin-lattice relaxation, spin-spin relaxation determines the natural width of the lines in the spectrum. This is normally defined in terms of the half-height line width $v_{\frac{1}{2}}$, as shown in fig. 7. For a sample possessing a spin-spin relaxation time T_2, the natural half-height line width is given by:

$$v_{\frac{1}{2}} = \frac{1}{T_2}$$

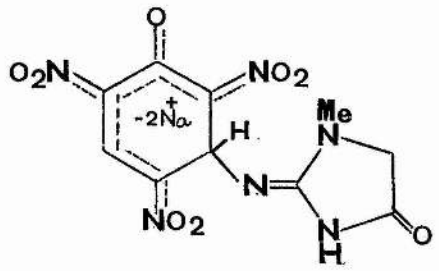
As both spin-lattice relaxation and spin-spin relaxation processes contribute to the width of a spectral line, the extensive delocalisation of charge of picrate ion in aqueous media may have tightened up ring protons in a solvation cage resulting in restricted rotation of the molecule, so properly orientated magnetic nuclei, which may effect spin-lattice relaxation, are present relatively



133 141

infrequently. However, we suggest that due to longer spin-lattice and spin-spin relaxation times, the peak height of the ring protons of picrate ion has suppressed. That is why picric acid in benzene, chloroform, acetone and DMSO displays a reasonable peak intensity but additon of H_2O/D_2O in these solvent reduces the peak height. The addition of alkali further aggravates the situation, reflecting the role of solvation resulting from the picrate ion that formed in the solution. If there had been deuterium exchange, one should have a triplet or at least a hump in carbon-13 nmr spectra (see experimental section) and a reasonable peak in proton nmr spectrum when H_2O is used as solvent. Hence, carbon-13 and proton nmr studies completely remove the idea of deuterium exchange under our experimental conditions.

Creatinine behaved differently in neutral and alkaline media. Proton nuclear magnetic resonance studies in D_2O had two absorptions at δ 3.04 and 4.03 ppm, relative to trimethylsilane, owing to the methyl and methylene protons. The proton of the NH group had exchanged with deuterium. On addition of NaOD, the absorption at δ 4.03 ppm disappeared which indicated that creatinine was in rapid equilibrium between the enol and keto forms (133, 141). Butler (1975) reported that the carbanion of creatinine attacked the unsubstituted positions of picric acid to give (135) and (136) and Vasiliades (1976) claimed that it was enolate anion of creatinine which involves in the formation of 1:1 complex. He suggested structures (134) and (137). However, our findings do not agree with any one of these



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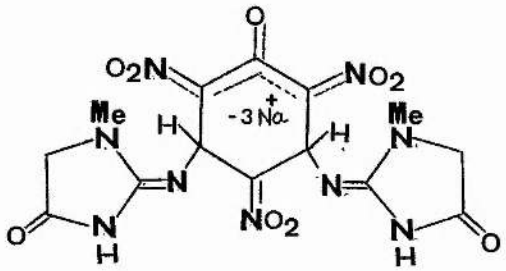

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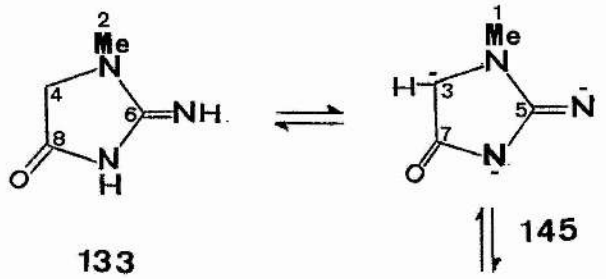
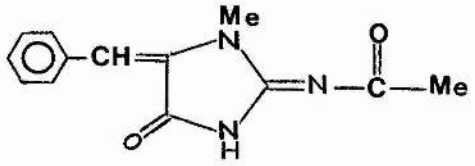


133 145

147 146

structures. There is, of course, another possibility that imino(C=$\bar{N}$) nitrogen may attack the meta positions of picric acid resulting in (142) and (143), and again our findings are inconsistent with structures (142) and (143).

However, it was decided to examine the behaviour of creatinine alone in neutral and in alkaline media. The carbon-13 nmr spectrum in water (H_2O,D_2O) exhibited four absorptions at δ 32.91, 59.09, 172.11 and 191.26 ppm respectively. The first two absorptions were assigned to -NMe and methylene (-CH_2-) groups and they split into a quartet and a triplet in the off-resonance spectrum. The last two remained unchanged and were attributed to imino-carbon and carbonyl groups. An aged solution did not show any deuterium exchange with methylene protons. However, on addition of a few drops of NaOH into aqueous creatinine solution, a series of lines emerged on the spectrum. After careful study of data, as mentioned in the experimental section, we found that, in addition to NH proton, sodium hydroxide had abstracted only one proton from methylene group and the resulting trianion (145) remained in equilibrium with the starting material (133). That is why, two -NMe absorptions were observed at δ 31.12 (C_1) and 37.46 (C_2) ppm. A collection of five lines resulting from C_3 (doublet) and C_4 (triplet) was also seen in the off-resonance spectrum. C_3 resonated at δ 54.81 while C_4 at 57.14 ppm. Besides this, C_5, C_6, C_7 and C_8 absorbed at δ 162.25, 173.68, 177.81 and 187.92 ppm respectively, and they remained unsplit in the off-resonance spectrum. All the carbons pertaining to structure (145) moved upfield compared to the carbons of



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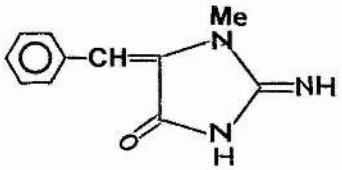

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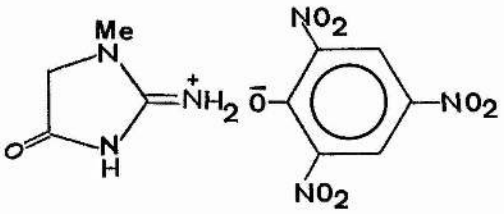
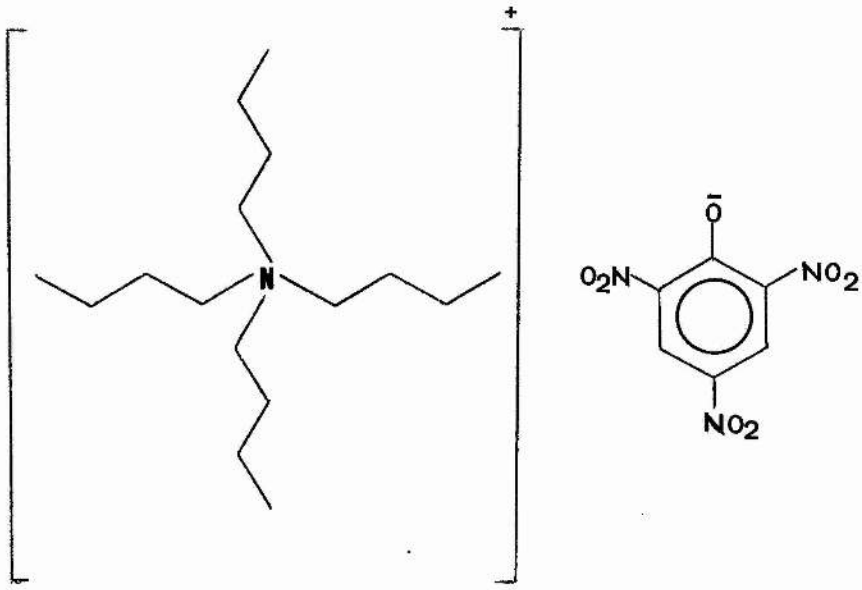


150

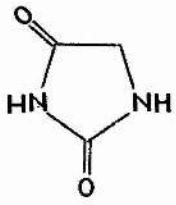
structure (133). This study unambiguously indicates the maximum population of structures (133) and (145) in solution. Moreover, resonances belonging to C_9 and C_{10} were not seen which reflected that probably species (146) and (147) were in a very low concentration or did not exist, although theoretically, their existence is possible. Removal of both hydrogens from methylene group in presence of protic solvent seems to be unlikely. Despite this, when creatinine spectrum in D_2O + NaOD was taken, a broad hump resulting from attack of deuterium at methylene carbon (C_3) came up while other absorption peaks remained unaffected.

There is, of course, another possibility. Does creatinine skeleton remain intact or rupture in a basic media? We found that there was no change in creatinine structure when it was stirred in 5% sodium hydroxide solution at room temperature. The material was recovered unchanged and showed no depression in mixed melting point. Even during hydrolysis of compound (148) with concentrated sodium hydroxide the creatinine skeleton remained intact and the resulting product (149) was identified by all means. Thus, the facts so far we have obtained, reflect creatinine in a basic media behaves as a molecule with two nucleophilic centres, ie. carbanion and imino nitrogen anion ($=\bar{N}$) are both involved in the formation of complex (138).

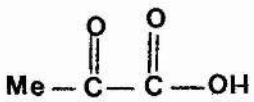
Complex (138) is very soluble in water and on acidification of aqueous solution of (138) a red solid settled down (150).



151



152

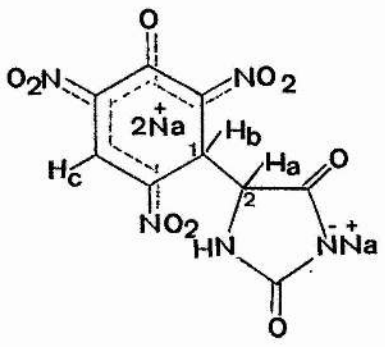


153

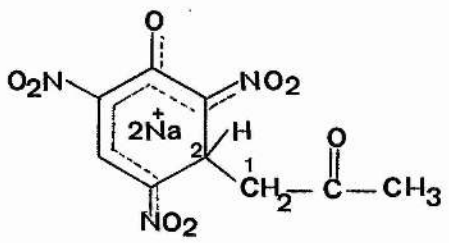
Greenwald and Gross (1924, 1928) also reported similar chemical changes. This red solid changed its colour to yellow when it was kept in an oven at 130-140°. Chemical, physical and spectral evidence indicate that there is no chemical bond formation in (150) but merely an electrostatic attraction between picric acid and creatinine. This picrate (150) is further confirmed by comparison with authentic sample. From the filtrate picric acid was recovered and proved by all means.

In another experiment, we tried to replace sodium cation by organic counterpart (phase-transfer catalyst). During vigorous shaking and multiple extraction, again we observed that compound (138) had fragmented and we could only isolate picrate of tetrabutylammonium (151). Its spectral data are give in the experimental section.

There are several functional groups on the creatinine molecule, any one of which may be involved in the Jaffé reaction. We tried our best to methylate nitrogens of creatinine, especially the imino group (=NH) but were unsuccessful. However, compounds like hydantoin (152) and pyruvic acid (153) were taken which had no imino group (C=NH) and acted as a molecule with single nucleophilic centre in alkaline media. Kammeraat (1978) reported interference of pyruvate and other α-keto compounds in the estimation of creatinine present in biological fluids. This piece of information also prompted us to look into the reaction of picric acid with alkaline solution of pyruvic acid. Compounds (152) and (153), both gave bright red powder which did not melt, so they must be salts. Their mass spectra were



155



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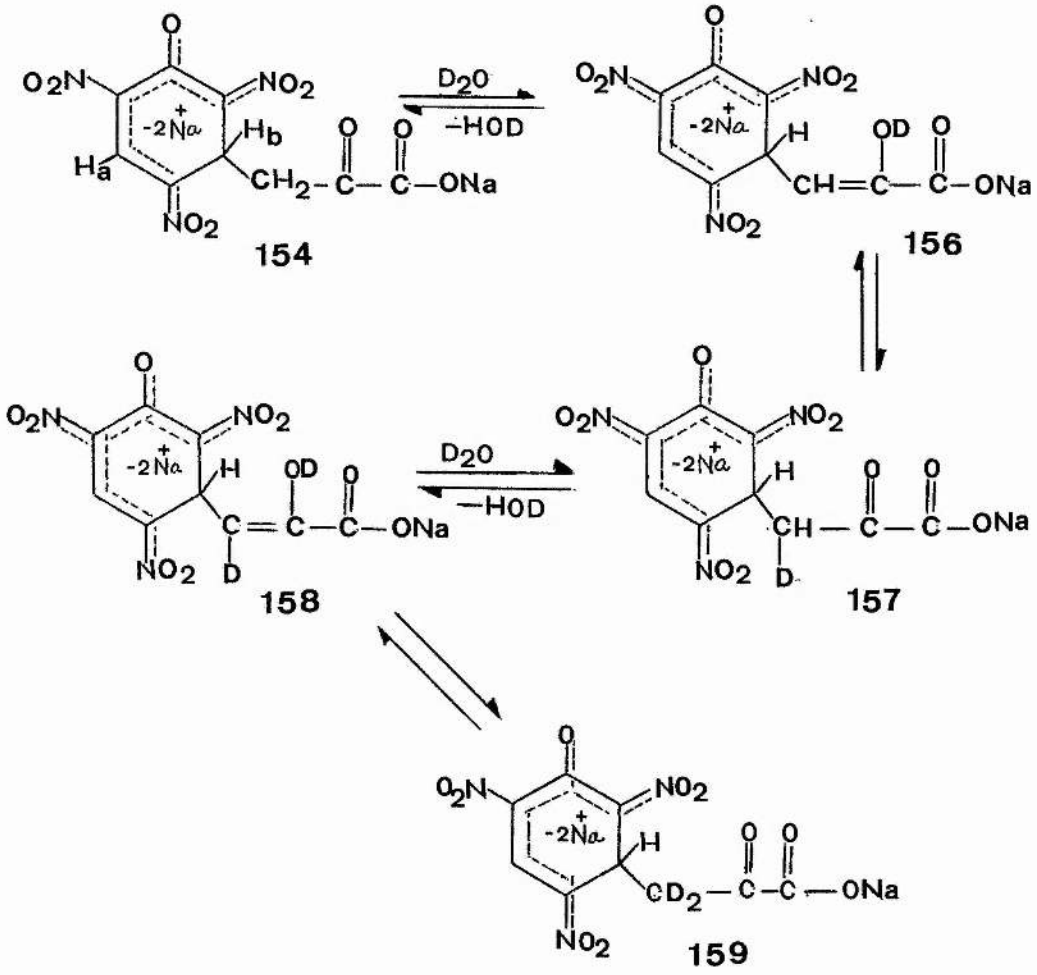


SCHEME 23

not informative. The characteristics of both were akin to (138). Elemental analysis and spectroscopic evidence suggested molecular formulae of $[C_9H_4N_3O_{10}]3Na$ (154) and $[C_9H_4N_5O_9]3Na$ (155).

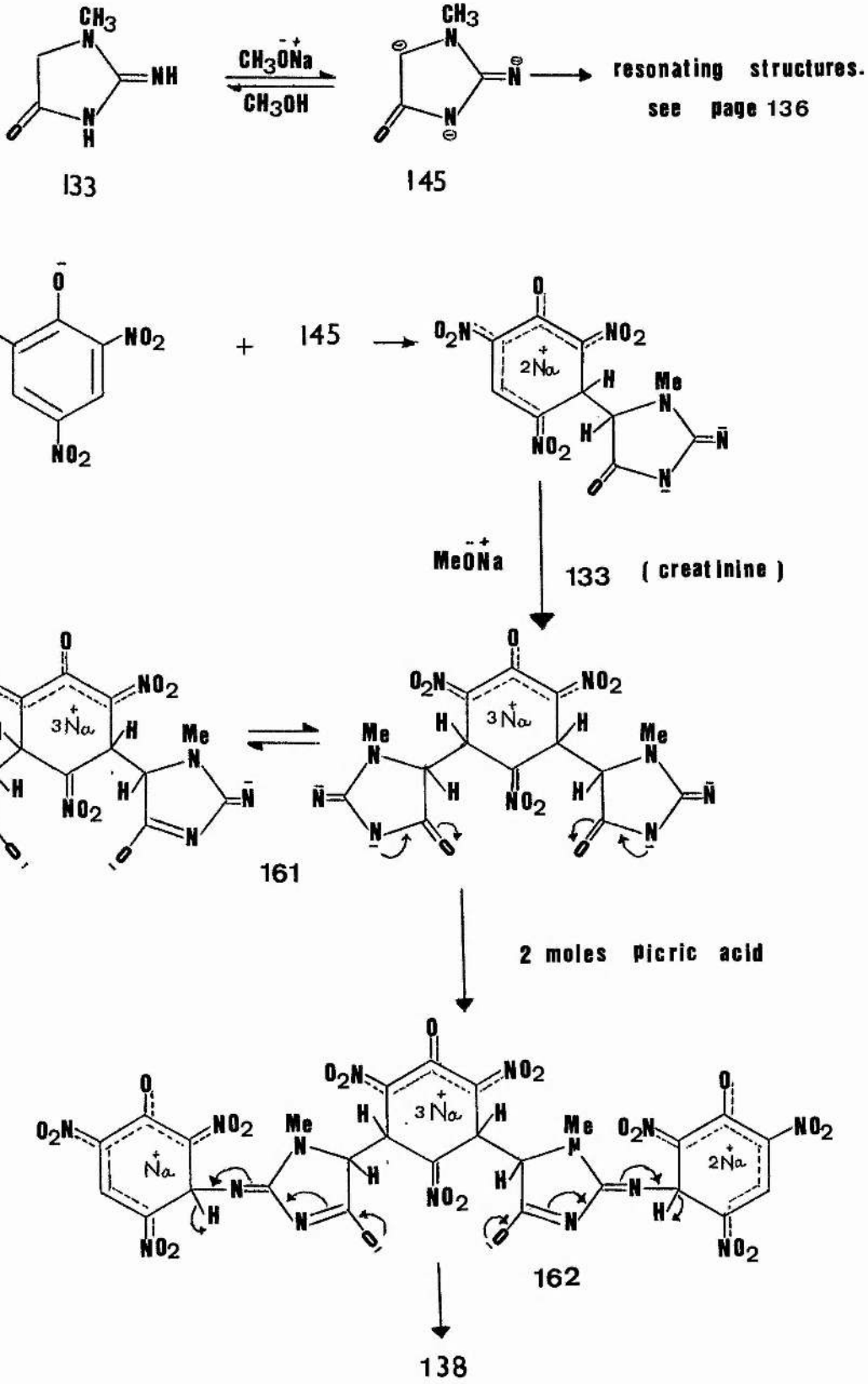
The proton nmr spectrum of (154) in D_2O at 100 MHz using benzene capillary as an external reference, exhibited two singlets at δ 9.14 and 4.93 ppm owing to protons H_a and H_b. No methylene protons were observed, only once at 60 MHz a doublet (due to $-CH_2-$ at δ 2.5 ppm) and a triplet (due to H_b at δ 4.93 ppm) were seen when the spectrum was taken on the spot using trimethylsilane as an external reference. This might be the cause of rapid exchange of methylene protons with solvent (D_2O). Sometimes a weak doublet at δ 5.97 ppm was observed which could be due to structure (156) as shown in Scheme 23. This doublet disappeared with time. In the carbon-13 nmr spectrum, using H_2O as solvent, methylene carbon resonated at δ 27.34 and the sp^3 and sp^2 carbons of phenyl ring absorbed at 49.55 and 127.97 ppm. These carbons split, respectively, each into a triplet and doublet. The carbonyl groups appeared at δ 141.94 and 163.35 ppm. Carbons containing nitro groups did not emerge and the reason for this disappearance has already been explained. Well dried sample gave no absorption above 3000 cm^{-1} while stretching vibration at 1590-1640 cm^{-1} was consistent with C=O groups in the ir spectrum.

The Meisenheimer complex of acetone-picrate (160) (Kabeya et al 1973) is included for comparison. In this case, there is little deuterium exchange with methylene protons and

all protons absorbed at their right places. The chemical shifts and shape of peaks in carbon-13 and proton nmr of (160) well resemble the Meisenheimer complex of creatinine, pyruvate and hydantoin as reported herein. Spectral data of (160) are given in the experimental section.

Compound (155) is extremely hygroscopic and exhibited a very broad band at 3400-3100 cm^{-1} which was assigned to NH/OH groups. It did not lose water even after prolonged drying in vacuum at 100°C. It seemed as the water had become an integral part of compound (155). The remaining portion of the ir spectrum was consistent with C=O and NO_2 groups.

In the proton nmr spectrum, there were two doublets and a multiplet. The doublets at δ 4.3 (J_{ab}=4 Hz) and 8.75 ppm (J_{cb}=5 Hz) were assigned to protons H_a and H_c. The multiplet at 5.36 ppm was attributed to proton H_b. The resonance lines were too close to measure the exact coupling constant for H_b ($J_{ba,bc}$=4 to 6 Hz). Here, the distinguishing features that we observed in this spectrum was allylic couplings, but this type of allylic coupling was not observed in compounds (154) and (160). Probably, steric restriction of rotation of carbon-carbon bond (ie. C_1-C_2) due to size of hydantoin had fixed the proton H_b at such an angle where it could easily be coupled with proton H_c, while free rotation in (154) and (160) did not permit allylic couplings. This observation suggests that structure (138) seems to be right. If structure (139) is assumed to be correct then it should exhibit allylic coupling like compound (155), but


CH3ONa
CH3OH
resonating structures.
see page 136
133
145
+ 145
MeONa
133 (creatinine)
161
2 moles picric acid
162
138

SCHEME 24

nothing like this was observed. Hence, we propose structure (138).

In the carbon-13 nmr spectrum, C_1, C_2 and C_3 resonated at δ 43.32, 60.88 and 128.01 ppm and each carbon was split into a doublet in the off-resonance spectrum. The carbonyl groups absorbed at δ 163.36 and 170.22 ppm and also remained unchanged in the off-resonance spectrum.

Hence, the studies of spectra data, physical and chemical properties of (154), (155), and (160) gave substantial support to structure (138) and confirmed that creatinine acted as a molecule with two nucleophilic centres in alkaline media.

Now we come to reaction mechanism of creatinine-picrate.(Scheme 24) The reactive part of the creatinine molecule is the methylene group, activated by the neighbouring carbonyl group, and the other functional group in the molecule is C=NH. In the presence of base both carbanion and imino anions are formed. As the carbanion is a better nucleophile than nitrogen anion, so carbanion first attacks the unsubstituted positions of picrate to give 2:1 complex (161). Butler (1975) also proposed the same complex on the basis of kinetic evidence. Greenwald and Gross (1924) Butler (1975) and Vasiliads (1976) reported that the full chromogenic value of the creatinine develops in the presence of excess picric acid. However, we suggest that complex (161) further undergoes reaction with picric acid, and here the nitrogen of imino group attacks the meta position of picrate ion to afford (162) which rearranges to (138) with removal of hydride

ion. Although imino anion is a poorer nucleophile than carbon, yet there are precedents where aliphatic as well as aromatic amines and other related amino compounds form Meisenheimer complexes with polynitro aromatic compounds (Buncel et al, 1968; Buncel and Webb 1974; Grudtsyn and Gitis, 1974; Buncel et al, 1974). The most puzzling thing in complex (162) is the removal of hydride ion which is difficult to explain. However, there is evidence of removal of hydride ion from the reaction of nitrobenzene and KOH. In this case, the presence of air or other oxidising agents encourage the elimination of hydride ion. Some conversion does occur in the absence of any added oxidising agent because nitrobenzene can act as its own oxidising agent (Sykes, 1977). So, there is no reason why picric acid, which belongs to the same class of compounds as nitrobenzene, should not facilitate the elimination of hydride anion and, to destroy it as formed. Moreover, the presence of methanol as a solvent in this reaction further helps in this connection. Recently, Makosza and Winiarski (1980) reported the migration of hydride anion from the aromatic carbon to the electron deficient carbon of the nucleophile in the reaction of nitro compounds with α-halosulphones, N,N-dialkyl-1-haloalkanesulphonamides and acetonitrile derivatives. In complex (138) we could not locate the hydrogen resulting from the hydride migration, but suggests probably, this hydride anion has migrated to unreacted picric acid which has been destroyed or washed away during washing of Meisenheimer complex (138) with methanol.

Butler (1975) reported that in the clinical determination of creatinine both the picric acid and creatinine are at fairly low

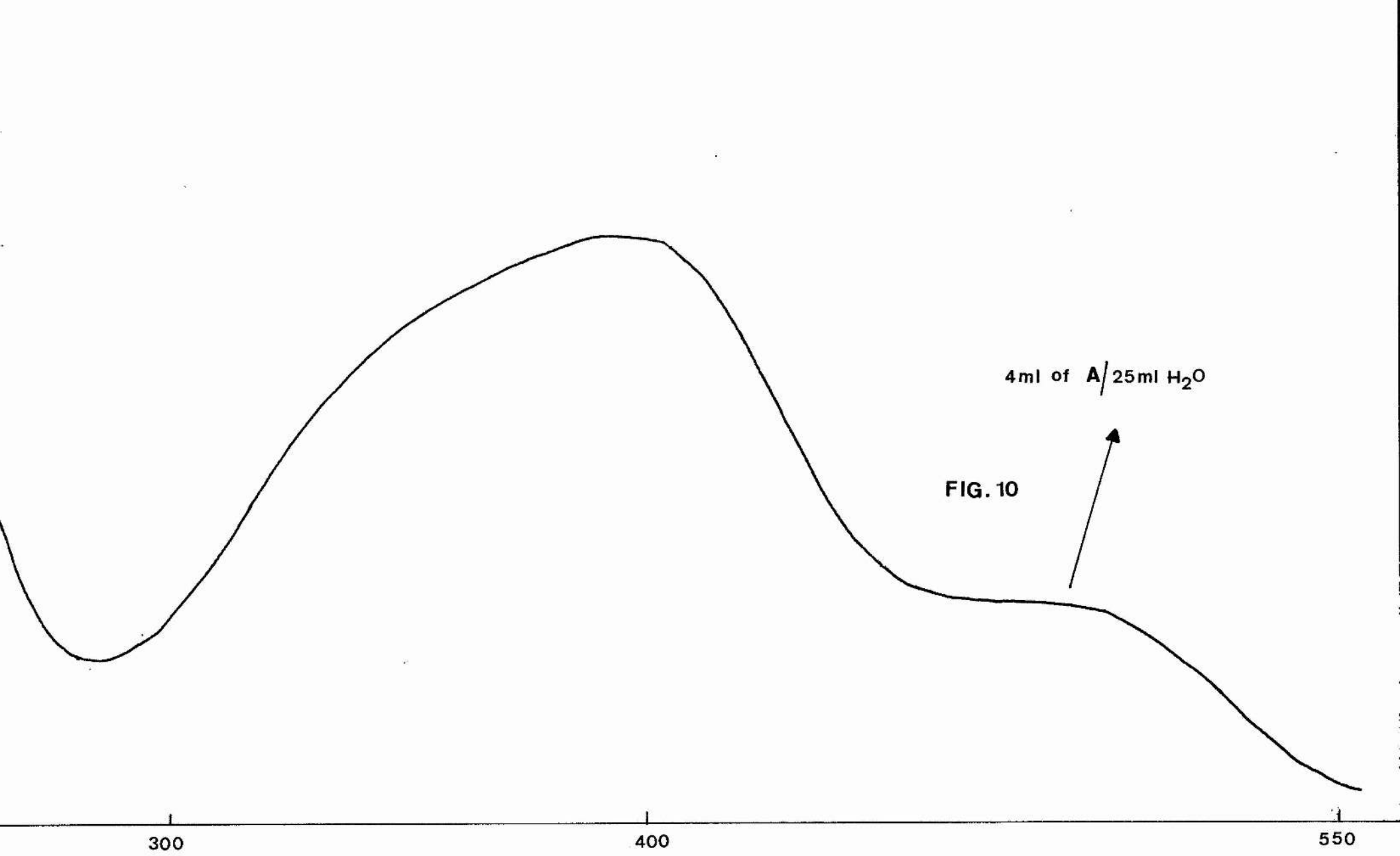


FIG. 10

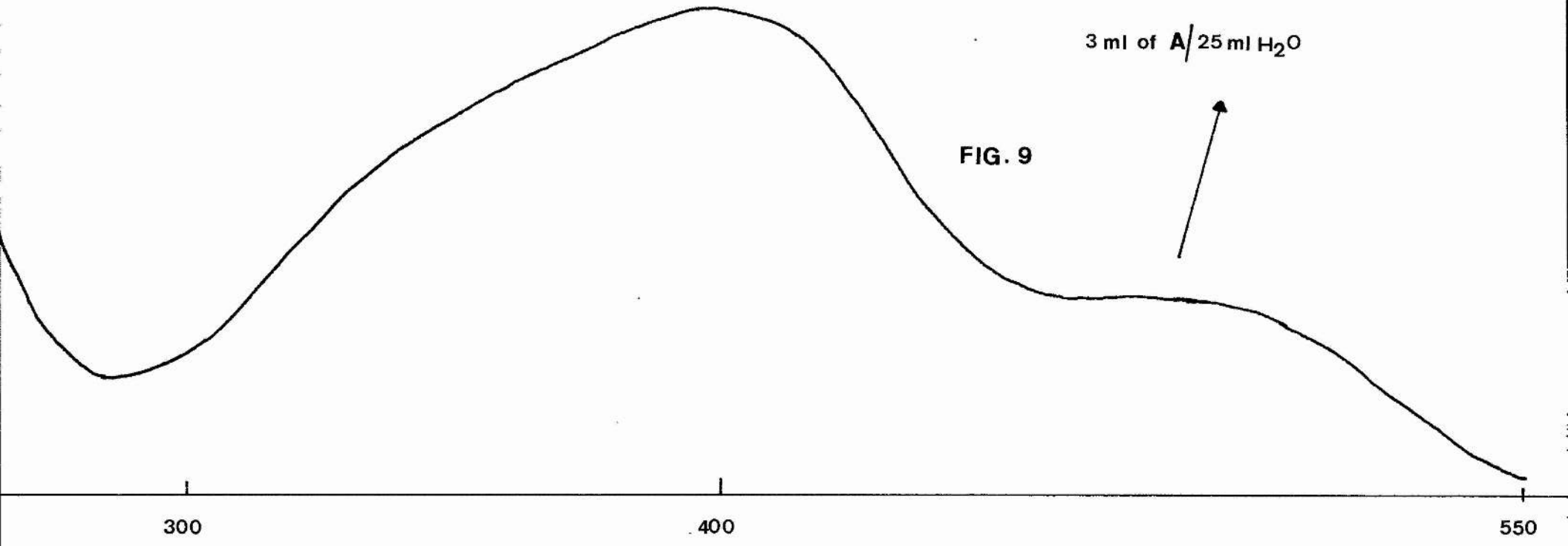


FIG. 9

COMPOUND(138) 0·02gm/100 ml H_2O = A

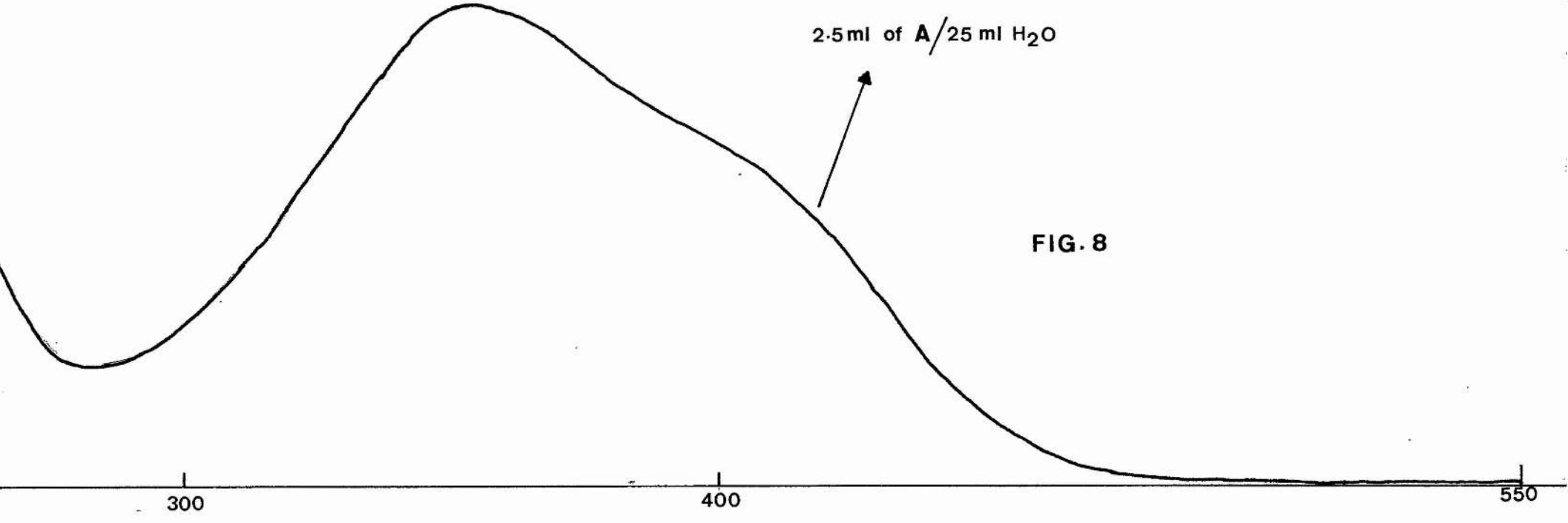
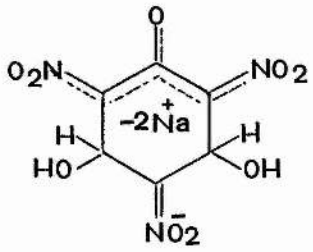
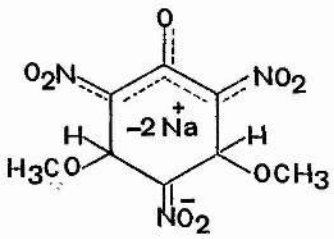


FIG. 8



163



164

low concentration and the red species formed under these conditions may not be the same as that precipitated from solution. We do not agree with this view because uv/visible spectra of compound (138) are exactly identical to that given by Butler (1975) and Vasiliodes (1976) in their publications. Again, Butler (1975) pointed out that a study of the spectral changes occurring during Jaffé reaction shows that addition of creatinine to alkaline picrate does not result in the formation of a new peak but broadening of that already present (470-550 nm). If the hydroxide ion present at high concentration the addition complex (163) is formed and it is this species which has such an intense absorption. However, the formation of (163) is likely, but we could not find any evidence of complex (164) which is analogous to (163). On the other hand, we have found that the absorption at 470-550 nm goes on increasing by increasing the amount of (138) in solution and the resulting spectra (Figs. 8-10) exactly coincide with that taken by Butler (1975) at various concentrations. It may be possible that complex (164) acts as an intermediate and consumes during the formation of (138). However, we do not associate the broadening of peak (470-550 nm) with formation of complexes (164) or (163).

After a detailed kinetic study, Butler (1975) observed a rate equation for the complex formation of the form:

$$\text{rate} = k\,[\text{creatinine}]\,[\text{picrate}]\,[OH]$$

The values of "k" obtained are 2.4, 2.3 and 2.3 $l^2 mol^{-2} s^{-1}$ and in all these cases picrate is in excess. When creatinine is in excess "k" is 9.3 $l^2 mol^{-2} s^{-1}$ which indicates that under these

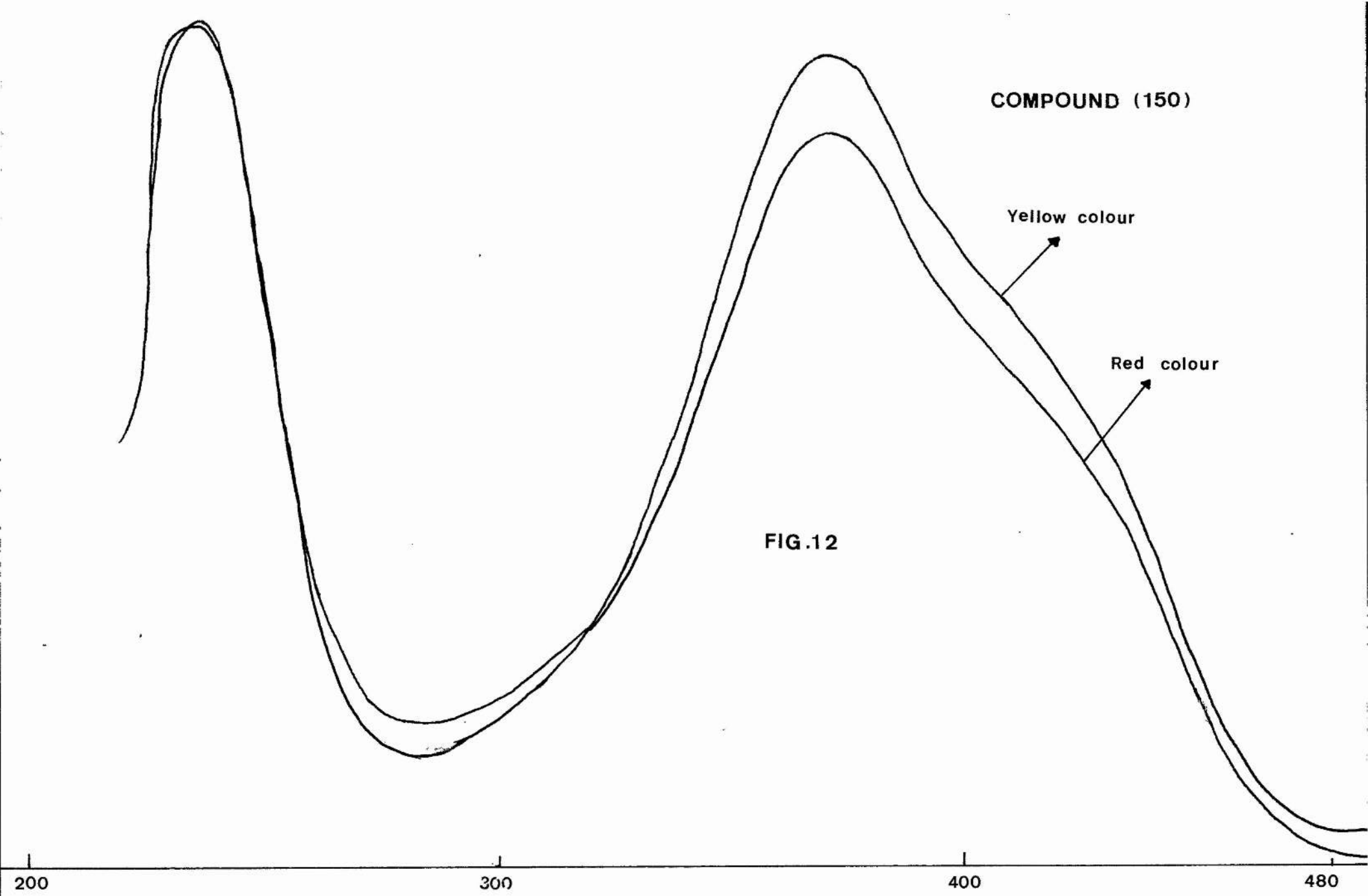
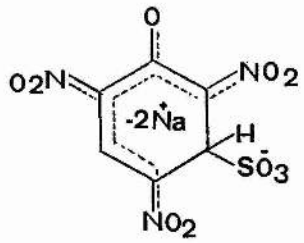
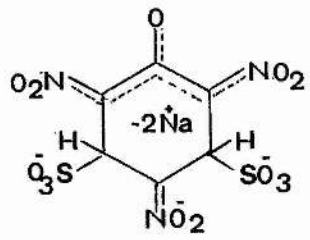


FIG.12



165



166

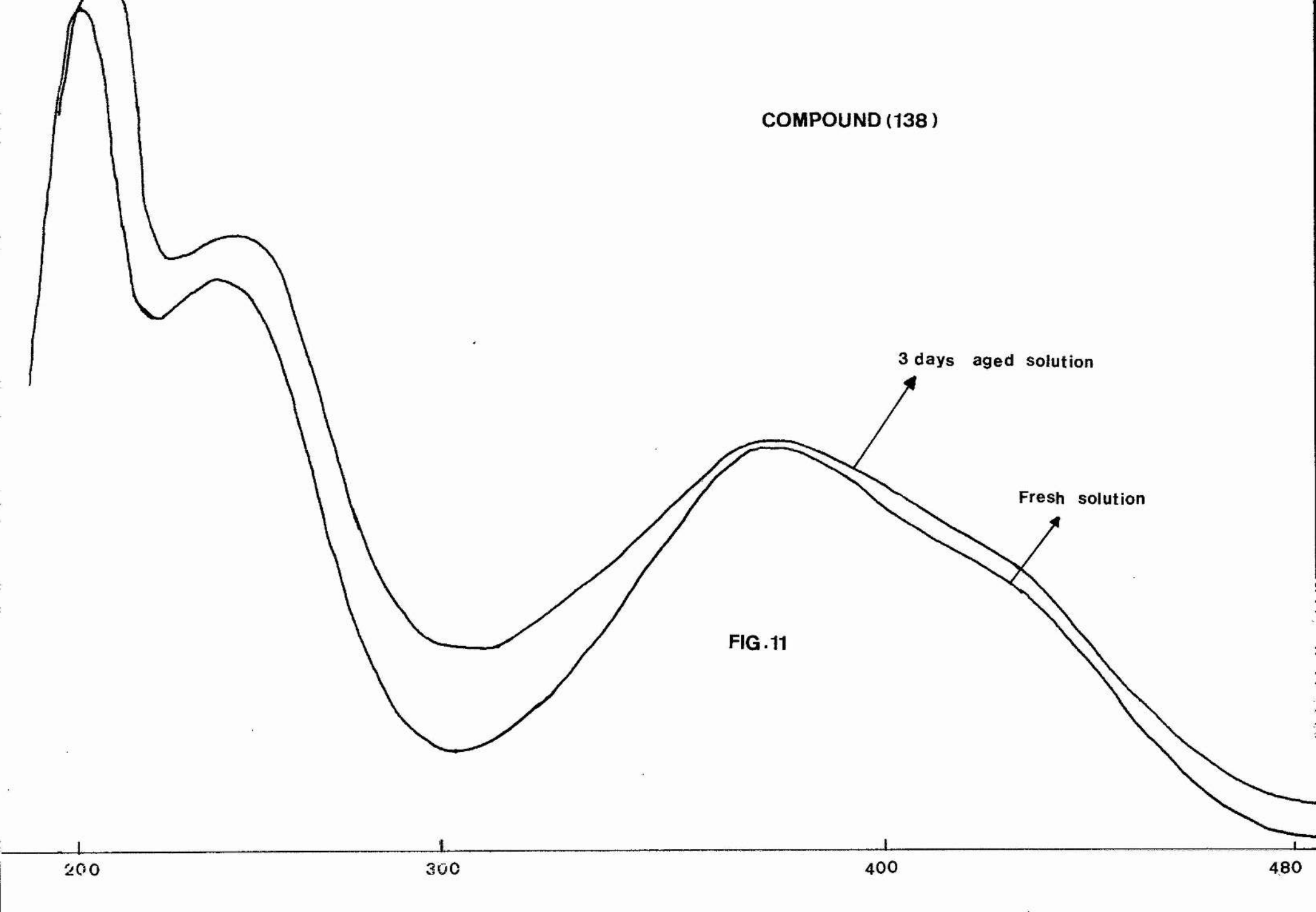
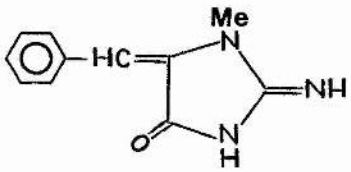

COMPOUND (138)
3 days aged solution
Fresh solution
200
300
400
480

FIG. 11

conditions there must be some slight change of mechanism. He estimated that one mole of each picric acid and creatinine are involved in the formation of complex in Jaffé's reaction. The red colour solution fades on standing which leads to the formation of 2:1 adduct. But we have found this is not the case. The uv/visible spectrum of (138) is recorded immediately on making solution and then after three days aged solution. The colour does fade but no spectral change is seen and found to be identical in every respect (Fig. 11). If there is a change from 1:1 to 2:1 in the formation of adduct as described above, then one should have spectral changes because analogous Meisenheimer complexes resulting from sodium sulphite and picrate in ratio of 1:1 (165) and 2:1 (166) (Crampton and Ghariani, 1969) have different absorption spectral behaviour. Similar kind of spectral difference in the case of acetone-picric acid complexes, was also reported by Kabeya (1973). There is, of course, another possibility that strikes one's mind. Does complex (138) break up immediately in aqueous media and the fading of colour (red to yellow) is the cause of internal rearrangement of fragmented species or the whole molecule (138) itself rearranges without disintegration and do not affect the initial and final uv/visible spectra? As has been described previously, red and yellow coloured picrates of creatinine (150) were obtained by acid hydrolysis of complex (138). Both display absolutely identical uv/visible spectra (Fig. 12) and these spectra do not coincide with the spectra of (138) (Fig. 8) in every respect whatever the aged solution may be. The spectrum of pure picric acid almost

76



149

resembles the spectrum of picrate of creatinine. However, we suggest that fading of colour does not accompany any chemical transformation in complex (138).

We tried to find such a compound which should contain imino (=NH) group with structure skeleton similar to that of creatinine, but was unsuccessful. However, compounds (76) and (149) consist of imino group and we thought they could react with picric acid in a similar fashion as creatinine, which in turn, would provide direct proof for the reaction of imino group. We did not find anything like that except picrates of these compounds. Hence, after working on this tedious problem in every respect, we are certain that compound (138) is responsible for red colouration in Jaffé reaction, but not compounds (134), (135), (136), (137) and (150) as described previously by various workers.

EXPERIMENTAL

i) Freshly cut sodium metal (0.6 g) was dissolved in anhydrous methanol (50 ml) and creatinine (1.13 g) added. On slightly warming and shaking the solution became clear. A solution of picric acid (2.29 g) in anhydrous methanol was added dropwise with constant stirring, at room temperature, during 3 h. A bright red solid settled out. It was washed with anhydrous methanol and dried which gave Meisenheimer complex of creatinine-picric acid (138).

It does not melt and gives no molecular ion peak as it is an involatile salt. ν_{max} 1640-1610 (C=O) and 1580-1560 cm^{-1} (C=N) δH [D_2O] 3.61 (3H, s), 3.89 ($2H_c$, d), 3.96 (3H, s), 6.15 ($2H_d$, 2d) and 9.60 ppm (2H, s), δC [D_2O] 30.87 and 31.95 (2q overlap), 41.59 (d), 43.13 and 43.35 (2d overlap), 119.38 (s), 127.89 (d), 141.88 (s), 170.00 (s), 171.93 (s), 188.96 (s), 189.35 (s) and 189.68 (s) ppm (Found: C, 29.25; H, 2.46; N, 20.38; Na, 14.15 . $C_{26}H_{12}N_{15}O_{23}7Na$ requires C, 29.36; H, 1.13; N, 19.76; Na, 15.13%) It is hygroscopic and gains weight during weighing.

ii) Complex (138) (2.0 g) was dissolved in water (20 ml) and slightly acidified with hydrochloric acid. On standing a red solid settled out. It was washed with water, ether and then dried, m.p. 213° (150). The filtrate was yellow in colour, and extracted with ether which gave pure picric acid.

Picrate of creatinine (150) (2 g) in a dish was kept in an oven at 130-140°. The red colour changed into a yellow one,

m.p. 213°, and there was no depression in mixed m.p.

M.p. 213°, m/e 229 and 113 (M^+), ν_{max} 3320-3300 (NH) 1795 (C=O), 1700-1696 (C=N), 1635 and 1600 (C=C), 1560 and 1540 cm^{-1} (NO_2), δH([$^2H_6$]DMSO) 3.21 (3H, s), 4.34 (2H, s) and 8.72 ppm (2H, s). Protons NH have exchanged with solvent, δC([$^2H_6$]DMSO) 31.17 (q), 54.02 (t), 125.21 (d), 141.78 (s), 157.46 (s), 160.85 (s) and 171.18 (s) ppm. (Found: C, 35.05; H, 2.74; N, 24.72 $C_{10}H_{10}N_6O_8$ requires C, 35.09, H, 2.94; N, 24.55%)

iii) Tetrabutylammonium bromide was added into an aqueous solution of Complex (138) with vigorous shaking. A red substance was extracted with chloroform. On solvent removal, red crystals were obtained; they were recrystallised several times from ethyl acetate and then with chloroform which gave picrate of tetrabutylammonium (151).

M.p. 74° (not sharp), m/e 242 and 229 (M^+), ν_{max} 1610 and 1630 cm^{-1} (C=C), 1550, 1515, 1360 and 1300 cm^{-1} (NO_2), δH($CDCl_3$) 0.98 (12H, t), 1.26-1.80 (16H, m), 3.32 (8H, t) and 8.74 (2H, s) ppm. δC($CDCl_3$) 13.58 (q), 19.73 (t), 24.00 (t), 58.96 (t), 125.19 (s), 126.20 (d), 142.23 (s) and 162.11 (s) ppm (Found: C 56.30; h, 8.23; N, 11.49 $C_{22}H_{38}N_4O_7$ requires C, 56.15; H, 8.13; N, 11.90%)

iv) An anhydrous methanolic solution of picric acid (2.29 g) was added dropwise to a basic solution of pyruvic acid (0.88 g) (dissolved in a mixture of CH_3ONa + CH_3OH) with constant stirring at room temperature for 24 h. A red product was

filtered off and washed thoroughly with anhydrous methanol which gave the Meisenheimer complex of pyruvic acid (154).

It does not melt, ν_{max} 1640-1590 cm^{-1} (C=O) $\delta H(D_2O)$ 4.93 ($1H_b$, s) and 9.14 (1H, s) ppm, at 60 MHz once a doublet at 2.5 (due to $-CH_2-$) and a triplet at 4.93 ppm (due to H_b) were observed when the spectrum was taken immediately using trimethylsilane as an external reference. Sometimes a weak doublet at 5.97 ppm by virtue of structure (156) was seen, but disappeared with the passage of time, $\delta C(H_2O)$ 27.34 (t), 49.55 (d), 127.97 (d), 141.94 (s) and 163.35 (s) ppm (Found: C, 26.47; H, 1.52; N, 8.81; Na, 18.0 $C_9H_4N_3O_{10}3Na$ requires C; 28.21; H, 1.05; N, 10.96; Na, 18.0%) It is hygroscopic and gains weight during weighing.

v) Reaction of hydantoin (1 g) with picric acid (2.29 g) using similar conditions as described above gave the Meisenheimer complex of hydantoin-picric acid (155).

It does not melt, ν_{max} 3100-3400 (NH/OH) and 1715 cm^{-1} (C=O), $\delta H(D_2O)$ 4.3 ($1H_a$, d, J_{ab} 4 Hz), 5.36 ($1H_b$, m, $J_{ba, bc}$ 4 to 6 Hz), 8.75 ($1H_c$, d, J_{cb} 5 Hz), NH exchanged with solvent, $\delta C(H_2O)$ 43.32 (d), 60.88 (d), 128.01 (d), 163.36 (s) and 170.22 (s) ppm (Found: C, 24.54; H, 2.43; N, 15.86; Na, 15.66. $C_9H_4N_5O_9 3Na.3H_2O$ requires C, 24.06; H, 2.24; N, 15.59; Na, 15.36%). It is hygroscopic and gains weight during weighing.

vi) Meisenheimer complex of acetone-picric acid (160) was prepared by known method (Kabeya et al 1973).

It does not melt, ν_{max} 1670-90 cm^{-1} (C=O), H([$^2H_6$]DMSO)

2.10 (3H, s), 2.50 (2H, d), 4.82 (1H, t) and 8.56 (1H, s) ppm, $\delta C(H_2O)$ 30.36 (q), 37.77 (d), 45.80 (t), 127.96 (d), 141.97 (s) and 154.50 (s) ppm, $\delta C([^2H_6]DMSO)$ 29.37 (q), 47.18 (t), 118.74 (s), 122.79 (s), 129.0 (s), 132.02 (d), 159.99 (s) and 170.64 (s) ppm. The resonance of sp^3 carbon of the ring has mixed with resonances of DMSO.

vii) NMR of picric acid in various solvents

$\delta H([^2H_6]acetone)$ 9.06 (s) ppm, $\delta H([^2H_6]benzene)$ 8.12 (2H, s) and 10.4 (1H, s) ppm. The peak at 10.4 ppm disappeared with addition of D_2O, $\delta H([^2H_6]DMSO)$ 8.62 (s) ppm, the peak height decreased with addition of D_2O, $\delta H(D_2O)$ 8.9 ppm, very small peak, $\delta H(D_2O + NaHCO_3)$ 8.9 ppm, $\delta H(D_2O + NaOD)$ 8.9 ppm, the peak intensity in alkaline media is smaller than neutral one, $\delta H(H_2O)$ 8.9 ppm, very small peak, $\delta H(H_2O + NaOH)$ 8.9 ppm, peak is smaller than previous one.

$\delta C([^2H_6]acetone)$ 126.56 (d), 138.71 (s), 153.21 (s) and 182.71 (s), $\delta C([^2H_6]DMSO)$ 125.98 (d), 129.83 (s), 141.77 (s) and 158.38 (s) ppm, $\delta C([^2H_6]DMSO + NaOD)$ 126.48 (d), 128.15 (s), 142.14 (s) and 162.52 (s) ppm, $\delta C([^2H_6]DMSO + H_2O$, 1:1) 127.02 (d), 130.79 (s), 141.61 (s) and 160.08 (s) ppm, $\delta C(H_2O)$ 129.93 (d) ppm, $C(D_2O)$ 129.88 (d) ppm, $\delta C(D_2O + NaOD$ or $NaHCO_3)$ 130.01 (d) ppm. Other carbons did not appear when neutral or alkaline water was used. ν_{max} 3100 (OH), 1630 and 1610 cm^{-1} (C=C).

viii) Carbon-13 nmr shifts of 2,4-dinitrophenol

$\delta C(CHCl_3)$ 121.33 (d), 121.91 (d), 131.67 (d) and 159.11 (s)

ppm, carbons containing nitro groups did not appear. Due to low solubility in H_2O, a lot of noise appeared; so it is not worthwhile to produce data, but carbon having nitro group did not emerge, same as is the case with 2,6-dinitrophenol.

ix) NMR of creatinine

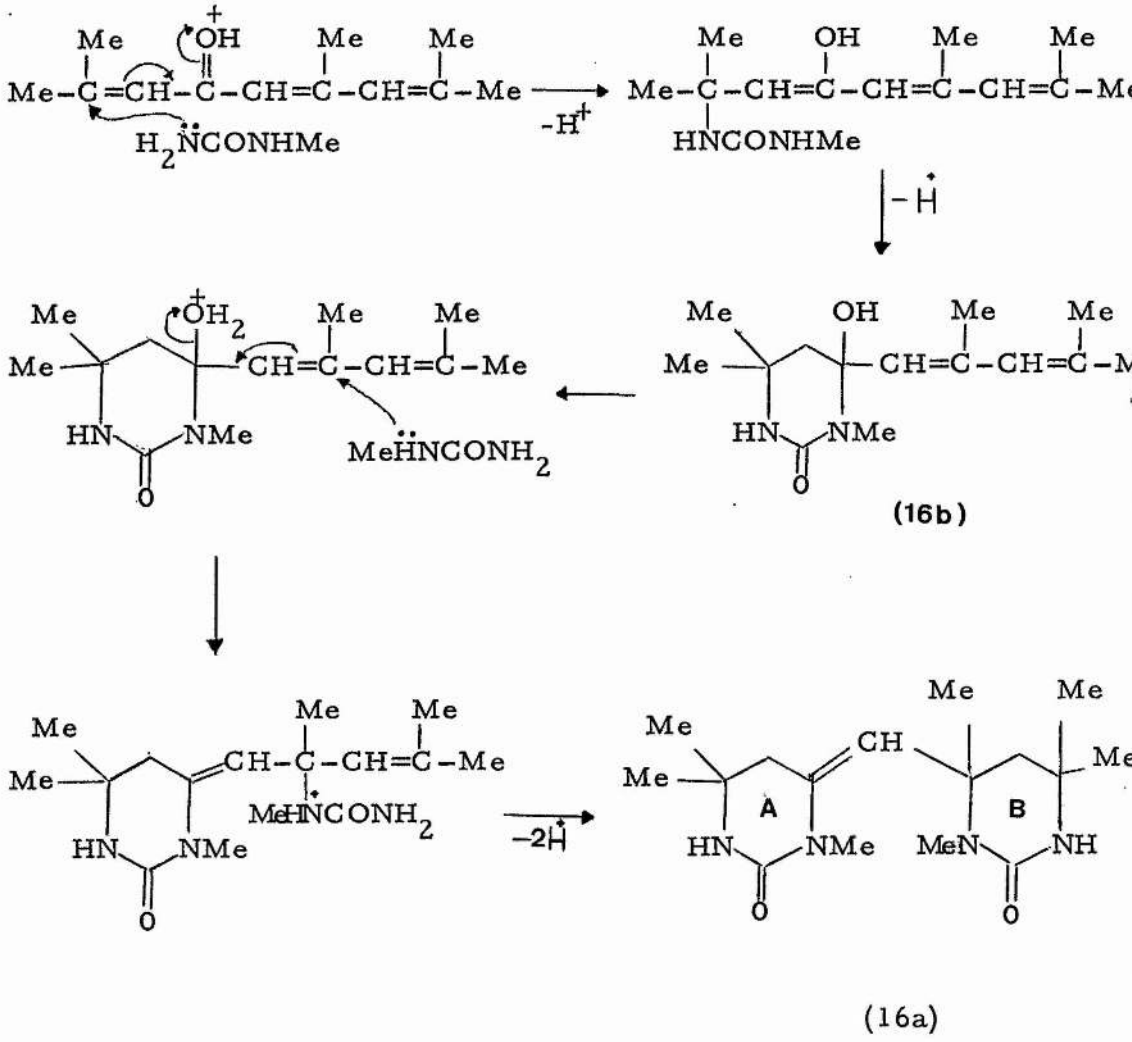
$\delta H(D_2O)$ 3.04 (3H, s), and 4.03 (2H, s) ppm, the peak at 4.03 ppm disappeared with addition of NaOD, $\delta C(H_2O)$ 32.91 (q), 59.09 (t), 172.11 (s) and 191.26 (s) ppm, $\delta C(D_2O)$ 32.93 (q), 59.13 (t), 172.17 (s) and 191.42 (s) ppm, $\delta C(H_2O + NaOH)$, 31.12 (q), 37.46 (q), 54.81 (d), 57.19 (t), 162.25 (s), 173.68 (s), 177.81 (s), and 187.92 (s) ppm, $\delta C(D_2O + NaOD)$, 31.0 (q), 37.28 (q), a broad hump appeared in place of methylene group, 161.49 (s), 172.95 (s), 177.40 (s) and 188.59 (s) ppm

x) Creatinine (2 g) in 5% sodium hydroxide was stirred at room temperature for 1 h. The resulting solution was neutralised with hydrochloric acid and then poured into excess acetone. A white solid settled out, washed with cold water, acetone and finally with ether. When dried, it had m.p. 260°, mixed m.p. 260°. The filtrate was reduced to dryness, nothing was obtained except a few crystals of sodium chloride.

xi) When above experiment was repeated with compound (148), another compound (149) was obtained but creatinine ring remained intact.

M.p. 338° (dec.), m/e 201 (M^+), ν_{max} 3290-3120 (NH), 1710 (C=O), 1665 (C=N), and 1630 cm^{-1} (C=C), $\delta C([^2H_6]DMSO)$ 27.77 (q), 113.24 (d), 127.63 (d), 130.04 (d), 133.81 (s), 135.04 (s), 166.31 (s) and 174.46 (s) ppm (Found: C, 65.40; H, 5.45; N, 20.92

$C_{11}H_{11}N_3O$ requires C, 65.65; H, 5.50; N, 20.88%)



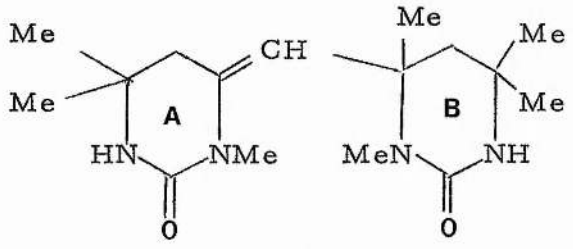
(16b)

(16a)

Scheme (2a)

APPENDIX

After this thesis had been typed we received information from Dr. M. Kaftory, Israel Institute of Technology, that, from an X-ray crystallographic study, the structure of product resulting from the reaction of 1-methylurea and mesityl oxide is (16a), which is different from that proposed previously.



(16a)

In light of the structure (16a), we propose a reaction mechanism in Scheme (2a) where $-NH_2$ part of 1-methylurea is involved in Michael condensation. No doubt, nitrogen of NMe group of the molecule seems to be more basic than NH_2, but it appears as the heavy protonation on NMe permits conclusively $-NH_2$ group to attack unsaturated carbon atom first followed by cyclisation leading to (16b). After that, protonation of species (16b) and an attack of NMe group, which is difficult to explain, gives the final product (16a).

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